Clinical Practice Pearls

Down Memory Lane

Founder Chairman Mr M Manal felicitates Dr Rustom Jal Vakil on his path-breaking work on hypertension published in the *British Heart Journal*.

The product used by Dr Vakil was Serpina (Himalaya).

The first Head of R&D of The Himalaya Drug Company, Dr Roshan M Captain (second from left) with Dr Rustom Jal Vakil (third from left), founder Chairman Mr M Manal (third from right) and other distinguished guests at the felicitation function.
The Himalaya Drug Company was founded by my father in 1930, long before I was born, with a clear vision to bring Ayurveda to society in a contemporary form. New formulations were created by referring to ancient Ayurvedic texts, selecting widely available Indian herbs and subjecting dozens of these herbs and combinations to modern pharmacological, toxicological, and safety tests to create new drugs and therapies. The most promising formulations then underwent clinical trials by doctors and institutions of modern medicine.

The breakthrough came in 1949 (after I was born!) when the *British Heart Journal* published the work of India’s pioneer in cardiology, Dr Rustom Jal Vakil. He researched *Rauwolfia serpentina*, the world’s first successful blood pressure lowering agent. The product Dr Vakil used for his work was Serpina (Himalaya)!

As an offshoot of this vision, in the year 1961, The Himalaya Drug Company started publication of the journal “Probe—Exploring ancient and modern medical learning” with the objective to provide latest research updates to the medical community. It was the belief of its publishers that, through high standards of medical journalism and usefulness, Probe would be accepted by doctors all over the nation.

Over the years, the readership of Probe increased in volumes and the publication spread its wings overseas. Today, Probe is read in more than 35 countries.

With great humility, I present to you the 50th anniversary issue of Probe. On this occasion, I thank you, our readers, for your kind support through the years, for your trust and prescriptions of Himalaya products and for being a part of this milestone moment.

Warm personal regards,

Meraj Manal
Chairman
Himalaya Global Holdings Ltd.
(Parent of The Himalaya Drug Company Worldwide)
meraj.manal@himalayaglobalholdings.com
Rauwolfia serpentina (Apocynaceae)

a.k.a. Sarpgandha (Sanskrit), Rauwolfia (English).

The pharmacological properties of Rauwolfia serpentina were discovered by the founder of The Himalaya Drug Company. This led to the introduction of Serpina®, the world’s first antihypertensive drug in 1934.
Clinical Insight

Safety and Efficacy of Cystone in Management of Ureteric Calculi: A Prospective Randomized Placebo-Controlled Study ............................................. 1
Efficacy and Safety of Cystone Syrup in Chronic Urinary Tract Infection: A Double-blind, Randomized, Placebo-Controlled Study ....................... 7
Urinary Tract Infection and its Management by Renalka ................................. 13
Urinary Tract Infection in Postmenopausal Women ..................................... 15
Epidemiology of Pediatric Urolithiasis ......................................................... 21
Clinical Characteristics and Risk Factors for Septic Shock in Patients Receiving Emergency Drainage for Acute Pyelonephritis with Upper Urinary Tract Calculi ........................................... 27

Abstracts .................................................................................................. 29

Drug Alert ............................................................................................... 43

Case Discussion ....................................................................................... 44

Tech Bytes .............................................................................................. 47

Drug Info

Cystone® (SYRUP) .................................................................................. 48
Cystone® (TABLET) ................................................................................ 50
Renalka® (SYRUP) .................................................................................. 52

Patient Education

Kidney stones ........................................................................................... 54

Herbal Notes

Allium sativum ......................................................................................... 58
Terminalia arjuna ..................................................................................... 58
Hemidesmus indicus ............................................................................... 59
Achyranthes aspera ................................................................................ 59

Liv.52 Update

Evaluation of Efficacy and Safety of Liv.52 HB Capsules in Chronic Hepatitis B: Double Blind, Randomized, and Placebo-Controlled Clinical Study ......................... 61
Contents

Review ......................................................... 68
Quiz Corner ............................................... 70
History of Medicine .................................. 71
From Other Pages .................................. 72
Miscellaneous

Laughter, the best medicine ................................. 76
Think Wise .................................................. 76

Special Features

Health Benefits of Green Tea—A Review ................ 39
Herb Profile: Bacopa monnieri ......................... 42
Upcoming Events ........................................ 46
Doctors’ Feedback ....................................... 66
About Himalaya ......................................... 74

For subscription requests and other communications:

The Managing Editor—Probe
Scientific Publications Division
The Himalaya Drug Company
Makali, Bangalore 562123

Email: publications@himalayahealthcare.com
Clinical Insight

Safety and Efficacy of Cystone in Management of Ureteric Calculi: A Prospective Randomized Placebo-controlled Study

Mohanty NK, et al.


**ABSTRACT**

Medical management of urolithiasis is still a challenge for modern medical practice. In the present study, Cystone tablet, an Ayurvedic formulation claimed to be useful in urolithiasis, was evaluated for its safety and efficacy in reduction or expulsion of ureteric calculi and to assess the role of Cystone in relieving the clinical symptoms.

This was a prospective randomized, double-blind, placebo-controlled trial amongst 52 patients with upper urinary tract calculi of 5 to 10 mm diameter. Patients were evaluated by plain abdominal film of the kidneys, ureter, and bladder (KUB) plus an ultrasound examination, for 6 months. Patients were equally divided into active treatment or placebo groups. The patients were advised to take Cystone or placebo at a dosage of 1 tablet, thrice daily for 6 months. Patients kept a record of number of pain episodes (severity of pain was assessed by Visual Analogue Scale [VAS]). In addition, other parameters such as fever, low backache, and decrease in frequency of urine were evaluated to assess the relief of clinical symptoms. Urinary microscopy and hematological parameters were also evaluated.

In active medication group, there was a significant reduction in the size of the calculi while there was an increase in the placebo arm. There was significant lower VAS score in the active medication arm as compared to placebo. On urine analysis, significant reduction in microscopic hematuria, pus cells (pyuria), bacteriuria, and crystalline sediments was observed. Significant reduction in the size of the stone and disappearance of the calculi was seen with Cystone treatment. There was no improvement in clinical symptoms or investigations in the placebo-treated subjects.

This study suggested that the Ayurvedic formulation Cystone tablet has a therapeutic promise in the management of ureteric calculi.

**Key words:** Urolithiasis, ureteric calculi, Ayurvedic formulation, Cystone

**Introduction and Aim**

Humankind is known to be suffering from urinary stone disease, which was first noticed in Egyptian mummies dated 4800 BC. Hippocrates in the 4th century BC noted renal stones together with a renal abscess and wrote in the Hippocratic oath “I will not cut the stone.” Urolithiasis in its different forms is a frequently encountered urological condition. For many years it has been at the forefront of urology. This situation might have changed with the advent of new, less invasive approaches to the management of urinary calculi. Nevertheless, urinary stones continue to occupy an important place in everyday urological practice. Currently urinary stones affect 10% to 12% of the population with a peak incidence at 20 to 40 years of age.² It is one of the most common and painful urologic disorders of the urinary tract that affects more than 3 million people every year in the United States alone.³ The lifetime risk of developing urolithiasis ranges between 5% and 12% and significantly affects the economy and public health as it has a high rate of recurrence.⁴,⁵
Risk factors for developing urolithiasis include age, sex, diet, geographic location, genetic predisposition, and urinary composition. Apart from these, the anatomy of the upper and the lower tract might be contributing factor in predisposing an individual to urinary tract infection or stasis. Small urinary calculi pass out of the body without any clinical intervention. In several studies, it has been reported that spontaneous passage rates of urinary stones range between 70% and 98% for small (≤5 mm) distal ureteric calculi. However, size and location of the calculi play an important role in predicting spontaneous passage. Typical symptoms of acute renal colic are intermittent colicky flank pain that may radiate to the lower abdomen or groin, often associated with nausea and vomiting. Lower urinary tract symptoms such as dysuria, urgency, and frequency may occur as the stone enters the ureter. Large calculi associated with unbearable pain can be treated with ureteroscopy, extracorporeal shock wave lithotripsy, percutaneous nephrostomy, and surgery. Calcium channel blockers, adrenergic alpha antagonists, and steroids are effective in enhancing the passage of urinary calculi. Phytotherapy with medicinal plants is widely used worldwide as an alternative primary health care. Regarding the treatment of urinary stone disease, several medicinal plants are available. Since the plants are claimed to be nontoxic, low cost, available in rural areas, and culturally acceptable, their effectiveness in the treatment of urinary stones has been widely studied.

Herbal medicines have been used to help in urolithiasis through anti-inflammatory, diuretic, litholytic, antimicrobial, and antispasmodic actions, though many of these properties are speculative. Cystone tablet, one such Ayurvedic formulation, has been claimed for its safety and efficacy in urolithiasis. The principal herbs of Cystone tablets have undergone extensive studies and geographical source and harvest time for each of the herbal ingredients have been recorded. Good Agricultural and Collection Practice (GACP) was followed during the collection and manufacture of this Ayurvedic formulation. Botanical identification and Ayurvedic criteria for desired quality were in accordance with the guidelines of Pharmacopoeial Standards for Ayurvedic formulations and were carried out by a qualified chemist approved by the Food and Drug Administration. This formulation has been approved by regulatory authorities in India as an Ayurvedic formulation and is available for clinical practice for the past 60 years. This study was aimed to evaluate the efficacy and safety of Cystone tablets in patients with urolithiasis.

Materials and Methods

Study design

This was a randomized, placebo-controlled, double-blind, clinical trial carried out at the Department of Urology, Safdarjung Hospital (New Delhi), India, between January 2008 and March 2009, in accordance to the ethical guidelines of Helsinki. Allocation was concealed. The sample size of the study was 52, with 26 in each arm.

Inclusion and exclusion criteria

Patients of either sex aged between 18 and 65 years presenting with characteristic loin pain, vomiting, and fever; diagnosed with ureteric calculi (5–10 mm in size); and willing to sign the informed consent form and comply with the study procedures, were included in the study. Those with larger urinary calculi, renal and/or hepatic pathology, and any systemic disorder requiring other medications or surgery were excluded from the study. Pregnant and lactating women were not included in the study.

Study procedure

This study was carried out in 52 consecutive eligible patients out of 81 patients who attended the Urology Clinic at Safdarjung Hospital, New Delhi, India. The study protocol, case report forms (CRF), regulatory clearance documents, product-related information, and informed consent forms (in English and Hindi) were approved by the institutional ethics committee. The patients were informed about the study drug, its effects, duration of the trial, and overall plan of the study. They were included in the clinical study only after written informed consent were obtained from each of them. They were free to withdraw from the study if desired. Patients followed their ad libitum diet. Detailed clinical history was noted by interviewing the patients. Thorough clinical examination and symptomatic evaluation were carried out and the details were noted in CRF. Urolithiasis was determined clinically, the diagnosis was confirmed by plain x-ray of the abdomen followed by ultrasonography. The x-ray of kidneys, ureter, and bladder (KUB) and ultrasonography were used to calculate the surface area of each stone based on length and width. Largest diameter of a stone was considered instead of the surface area in ultrasonography evaluation. The cumulative diameter was calculated for subjects with multiple calculi. Patients were advised to take the Ayurvedic formulation, Cystone, or an identical placebo at a dosage of 1 tablet thrice daily orally for 6 months.
All patients were asked to maintain a record of number of pain episodes, while severity of pain was assessed on a visual analogue scale. Patients underwent clinical, hematological, and radiological evaluation on entry, at 3 and 6 months. The clinical symptoms like fever and low backache were scored using numerical scale. They were allowed to take Diclofenac 50 mg tablet in case of severe abdominal pain.

**Primary and secondary outcome measures**

The predefined primary outcome measures were effect on change in the number and size of stones, spontaneous passage of stone, and symptomatic relief. The predefined secondary outcome measures were incidence of adverse effects and patient compliance.

**Adverse events**

All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to study medication were predefined as “unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take <80% of the medication) was not regarded as treatment failure and reasons for noncompliance were noted.

**Statistical analysis**

Statistical analysis was carried out using Fisher’s exact test for presence or absence of various signs and symptoms. Repeated measures of ANOVA followed by Dunnett’s multiple comparison posthoc tests were used for analysis of hematological parameters. Pyuria was analyzed by repeated measures of ANOVA using Friedman test followed by Dunnett’s multiple comparison posthoc test. Calculi size before and after the treatment was analyzed using paired Students “t” test. Values are expressed as mean ± SD for hematological parameters, pyuria, and calculi size. Remaining parameters were evaluated by the incidence of symptoms. The minimum level of significance was fixed at P<.05. Statistical analysis was carried out using GraphPad Prism version 4.03 for Windows, GraphPad Prism Software, San Diego, California, USA.

**Results**

The demographic data of the patients on entry (Table 1) indicated that 38 males and 14 female patients with a mean age of 34.73 ± 10.09 years were included in the study. Out of the 52 subjects, 26 subjects each received either Cystone tablets or placebo in a randomized manner. With Cystone treatment, a significant (P<.0001) symptomatic relief from intermittent abdominal pain (58%), fever (92%), and low backache (54%) was observed (Table 2).

**Effect of Cystone on Glycolic Acid-induced Urolithiasis in Rats**


The present study was conducted to evaluate the effect of Cystone on experimentally induced urolithiasis in rats. The study included 40 male Wistar strain rats that weighed in the range of 180 g to 220 g. They were divided into 5 groups consisting of eight rats each. The rats in the group 1 acted as controls and were fed with commercial diet, whereas group 2 rats received a calculi-producing diet (commercial diet mixed with 3% glycolic acid) for 42 days. The group 3, 4, 5 rats received Cystone at the dose of 250, 500, and 750 mg/kg body weight, respectively, once a day orally along with the calculi-producing diet for the same duration. On day 42, a 24-hour urine sample was collected after the last doses of the assigned schedules were administered. On day 43, the rats were killed by cervical dislocation and their kidneys were processed for the estimation of calcium and oxalate levels. Results showed that glycolic acid had significantly increased the levels of calcium and oxalate in the kidney and total kidney weight. Also, the urinary levels of calcium, oxalate, and inorganic phosphorus were increased. Administration of Cystone had a dose-related effect on the reduction of lithogenic substances, following glycolic acid-induced urolithiasis. These results indicate the importance of Cystone in the prevention of disorders associated with kidney stone formation.
Mohanty NK, et al. Cystone tablet in the management of ureteric calculi

There was also an improvement in the frequency and flow of urine, though not significant. Urine analysis indicated significant ($P<.0001$) improvement in microscopic hematuria, pus cells, bacteriuria, and crystalline sediments (Table 3).

Disappearance of the calculi as seen by ultrasonography was noticed in 13 out of 26 patients (50%) treated with Cystone tablets ($P<.0001$) and a decrease in the size of the stone in the remaining subjects. In patients treated with placebo, disappearance of stone was noted in 2 out of 26 patients. Disappearance of the calculi by plain x-ray abdomen and pelvis was seen in 15 patients out of 26 patients (58%) treated with Cystone tablets ($P<.0001$). There was a decrease in the size of the stone in another 11 subjects. In patients treated with placebo, out of 26 patients, there was disappearance of stone in 2 patients (Table 4).

There was significant ($P<.001$) reduction in the pus cells (pyuria) at the end of treatment in Cystone group (Table 5). The study showed significant reduction in the calculi size from 10.56 ± 3.28 to 4.51 ± 6.30 mm (57%) at the end of the treatment in Cystone group ($P<.0001$) as compared to placebo (increase by 10.37%) (Table 6).

There were no changes in hematological parameters except for a significant decrease in ESR (Table 7). No adverse effects were either reported or observed during the study.

**Discussion**

There are a number of options for treatment of urinary calculi, including surgery, endoscopic procedures such as ureteroscopy, percutaneous nephrolithotomy, and extracorporeal shockwave lithotripsy. Patients invariably prefer a medical therapy for the advantage of convenience. Medications like calcium channel blockers, α-adrenergic blockers, and steroids are used but adverse effects compromise their long-term consumption. On the other hand, some herbal remedies have been used to treat urinary stone disease, although scientific principles have been lacking. With the understanding of many physiopathological features underlying urinary stone disease and the mechanism of herbal remedies that can have a role in the formation and treatment of urinary stones, phytotherapy might be an alternative treatment with an effective, safe, and
acceptable option. Although some oral medications have positive effects, they are not effective in all patients. Oral citrate is one of the most widely used medical therapies for preventing urinary stone disease. However, this drug is not tolerated by all patients and some patients are still active stone formers during this therapy. Due to the adverse effects of these drugs, alternative treatment modalities composed of herbal remedies have been the mainstay of medical therapy for thousands of years, especially in Eastern civilizations. Use of medicinal plants as a source of relief and cure from various illness is as old as humankind itself. Even today, medicinal plants provide a cheap source of drugs for majority of world’s population. Plants have provided and will continue to provide not only directly usable drugs, but also a great variety of chemical compounds that can be utilized as starting points for the synthesis of new drugs with improved pharmacological properties. World Health Organization has also emphasized development and utilization of herbal drugs and traditional medicines for the benefit of the world population, in terms of cost effectiveness and side effects of the drugs. The organization has also estimated that about 80% of the population living in the developing countries relies on traditional medicine for their health care needs.

Cystone is an Ayurvedic formulation designed and developed for the management of urolithiasis or renal calculi. Cystone came into existence in 1943 and since then, it has been in use all over the world for the management of urolithiasis and UTI.

Herbs like *Didymocarpus pedicellata* has been shown to have diuretic activity. Another herb, *Saxifraga ligulata*, is reported to have active principles like afzelechin and bergenin. Afzelechin and bergenin are tannins and possess astringent properties, which make them effective...

### Table 4. Effect of Drug Therapy on Radiological Investigation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cystone (n = 26)</th>
<th>Placebo (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>End of 3rd month</td>
</tr>
<tr>
<td>X-ray abdomen showing renal calculi</td>
<td>Present</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Renal ultrasonography showing renal calculi</td>
<td>Present</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>0</td>
</tr>
</tbody>
</table>

*P* value: <sup>a</sup>*P*<.0001 as compared to “at entry” value; <sup>b</sup>*P*<.0002 as compared to “3rd month” value; <sup>c</sup>*P*<.017 as compared to “3rd month” value.

### Table 5. Effect of Drug Therapy on Pyuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystone (n = 26)</th>
<th>Placebo (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>End of 3rd month</td>
</tr>
<tr>
<td>Pyuria</td>
<td>1.39 ± 0.85</td>
<td>0.58 ± 0.70&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*P* value: <sup>a</sup>*P*<0.01 as compared to “at entry” value; <sup>b</sup>*P*<.001 as compared to “3rd month” value. The values for pyuria was evaluated using 4-point scale: 0: Occasional to Nil; 1: ≤5; 2: 6-9; 3: ≥10.

### Table 6. Effect of Drug Therapy on Calculi Size

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystone (n = 26)</th>
<th>Placebo (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculi size in mm</td>
<td>10.56 ± 3.28</td>
<td>10.22 ± 4.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*P* value: <sup>a</sup>*P*<.0001 as compared to “at entry” value.

### Table 7. Effect of Drug Therapy on Various Hematological Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystone</th>
<th>Placebo</th>
<th>Cystone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.84 ± 1.18</td>
<td>11.82 ± 1.20</td>
<td>11.93 ± 1.67</td>
<td>12.44 ± 2.36</td>
</tr>
<tr>
<td>WBC (per cu.mm)</td>
<td>7438.00 ± 1552</td>
<td>7562.00 ± 655</td>
<td>7365.00 ± 582</td>
<td>8890.00 ± 1864</td>
</tr>
<tr>
<td>Polymorphs (%)</td>
<td>62.73 ± 6.08</td>
<td>62.38 ± 4.01</td>
<td>62.04 ± 3.63</td>
<td>64.84 ± 9.67</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>33.62 ± 5.93</td>
<td>34.15 ± 4.73</td>
<td>34.00 ± 3.81</td>
<td>38.64 ± 10.54</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.35 ± 2.00</td>
<td>2.85 ± 1.43</td>
<td>2.85 ± 1.29</td>
<td>2.78 ± 1.20</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>1.00 ± 2.00</td>
<td>1.00 ± 1.10</td>
<td>1.12 ± 1.56</td>
<td>1.22 ± 1.86</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>22.88 ± 11.27</td>
<td>19.62 ± 8.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18.19 ± 9.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.45 ± 13.38</td>
</tr>
</tbody>
</table>

*P* value: <sup>a</sup>*P*<.001 as compared to “on entry” value.

Mohanty NK, et al. Cystone tablet in the management of ureteric calculi
antimicrobial agents. Bergenin is a known diuretic and is helpful in dissolving kidney stones.24,25 The roots of <em>Rubia cordifolia</em> contain ruberythric acid, which has been proved to dissolve oxalate stones present in the urinary tract, thereby facilitating their expulsion without recourse to surgery.26–28 It also possesses astringent, antibacterial, and anti-inflammatory actions. The oil from the roots of <em>Cyperus scariosus</em> has been found to exhibit anti-inflammatory properties.24,29 Studies conducted on the extracts of <em>Cyperus scariosus</em> were found to have potent antioxidant activity. <em>Achyranthes aspera</em> has potent anti-inflammatory, astringent, demulcent, and diuretic activity.24 <em>Onosma bracteatum</em> is known to have diuretic action. It regulates urine output, acts as a demulcent, and provides soothing action. It is useful in bladder irritation and is a spasmylic.30 Hajrul Yahood bhasma is useful in bladder irritation and is a safe alternate in the management of urolithiasis. It brings about significant symptomatic relief and helps in expulsion of stones or reducing the size of the renal stones. No clinically significant adverse reactions were reported or observed during the study period. A further study in a larger population will be required to confirm the evidence seen in the present clinical study.

**Conclusion**

The present study indicates that Cystone tablet is an effective and safe alternate in the management of urolithiasis. It brings about significant symptomatic relief and helps in expulsion of stones or reducing the

**References**

Efficacy and Safety of Cystone Syrup in Chronic Urinary Tract Infection: A Double-blind, Randomized, Placebo-controlled Study


ABSTRACT

Various drugs are available for the management of chronic urinary tract infection but because of emergence of antibiotic drug resistance and toxic manifestations, these agents cannot be used in chronic conditions. In the present study, a polyherbal formulation (Cystone syrup) was evaluated for its efficacy and safety in the treatment of chronic urinary tract infection. This was a double-blind, randomized, and placebo-controlled clinical trial. A total of 100 patients with confirmed clinical diagnosis of chronic urinary tract infection were included in the study. At the initial randomization visit, a detailed medical history, with special emphasis on history of urinary symptoms (burning micturition, frequency of micturition, fever, dysuria, and hematuria) was obtained from all the patients. All the patients underwent a thorough systemic examination. Routine blood analysis, urinalysis, and culture were done for all the patients. Each patient received either Cystone syrup or placebo at a dosage of 2 teaspoonfuls twice a day after meals for 21 days. The outcome of each group was assessed by comparing burning micturition, frequency of micturition, dysuria with mild fever, and effect of study medication on urinary pathogens and pus cells. Data of 96 patients were available for analysis. There was significant reduction in the urinary symptoms after treatment with Cystone syrup. Out of 46 patients, urine of 44 patients became sterile after treatment with Cystone syrup. No adverse drug effects were reported during the entire study period. Therefore, it can be concluded that use of Cystone syrup is clinically effective and safe in the management of urinary tract infection.

Key words: Cystone syrup, chronic urinary tract infection, polyherbal formulation

Introduction

The normal flora of the human body are extremely important as a key part of host defense against infection and because of their influence on nutrition. However, persistent microbial infections caused by commensals are a rapidly expanding problem because of increased antimicrobial resistance. This trend is particularly concerning because of the increasingly appreciated role that chronic infections may play in cancer and chronic inflammatory diseases.

Urinary tract infection can be restricted to the bladder with only superficial mucosal involvement, or it can involve a solid organ. Females are more prone to urinary tract infection because of shorter urethra and defect in local defense which makes them vulnerable to periurethral colonization. This defect may be due to a lack in a particular antibody and another reason may be the virulence of the particular strain of bacteria. In men, prostatic fluid inhibits bacterial growth and the mucus in the bladder has antimannose activity which discourages bacterial growth. Other risk factors of urinary tract infection include use of spermicidal agents and contraceptive diaphragm, comorbid diabetes and catheterization, obstruction of the urinary tract, and analgesic nephropathy. About 50% of all women will have an episode at
some point in their lifetime, and 20% to 30% will have a recurrence within 3 to 4 months of the acute infection.8 Urinary tract infection account for >100,000 hospital admissions annually, most often for pyelonephritis and they also account for at least 40% of all hospital-acquired infections and are in the majority of cases catheter-associated.9–12 Nosocomial urinary tract infections comprise perhaps the largest Institutional reservoir of nosocomial antibiotic resistant pathogens.13

Uncomplicated urinary tract infection involves the urinary bladder in a host without underlying renal or neurologic disease. Complicated urinary tract infection occurs in a patient with underlying structural, medical, or neurologic disease. Most pathogens responsible for urinary tract infection are Enterobacteriaceae with a high predominance of *Escherichia coli* (>80% cases). Other strains are less common, including *Proteus mirabilis* and more rarely Gram-positive microbes. Reinfection accounts for about 80% of recurrent infection. Uropathogenetic *E. coli* has virulent features like increased adherence to cells, resistance to bactericidal human serum, and K capsular antigen which is antiphagocytic and causes persistent infection in patients with recurrent cystitis.14 Recurrent urinary tract infection could also be due to obstruction of urinary tract, vesicoureteric reflux, renal calculi, diabetes mellitus, polycystic kidneys, prostatitis, pregnancy, neurogenic bladder, benign prostatic hyperplasia, and uroterovaginal prolapse in females. Dysuria, urinary urgency and frequency, nocturia, hematuria, fever, chills, and back or flank pain are the most common symptoms associated with urinary tract infection.

Urine analysis is performed as an initial diagnostic procedure for urinary tract infection. Midstream collection is the most common method of urine sampling used in adults. The urine test strip is commonly used for the qualitative diagnosis of urinary tract infection. This test detects leukocytes and nitrates. Simultaneous detection of the two is highly suggestive of urinary tract infection. This test is 95% sensitive and 75% specific, and its negative predictive value is close to 96%.15 However, this test does not detect *Staphylococcus saprophyticus*, a strain responsible for some 3% to 7% of urinary tract infections. Bacterial and leukocyte counts are examined using a dip-slide method. Normal values for a midstream specimen are less than or equal to 105 *E. coli* organisms and 104 leukocytes per milliliter. Urine microscopy is indicated despite a negative result of the urine test strip in patients with symptoms suggestive of urinary tract infection. A positive result on the nitrate test is highly specific for urinary tract infection, typically because of urease-splitting organisms, such as *Proteus* species and, occasionally, *E. coli*. Renal function testing is not indicated in most episodes of urinary tract infection. It may be helpful in patients with known urinary tract structural abnormality or renal insufficiency. In majority of patients with urinary tract infection, no imaging studies are indicated. However, if findings are suggestive of nephrolithiasis complicating the presentation, a noncontrast computerized tomography (CT) of kidney, ureter, and bladder or CT urogram should be obtained to exclude the possibility of obstruction or hydronephrosis. Every episode of a urinary tract infection has the potential to become a recurrent or chronic disease.

Patient education is important in the management of urinary tract infection. Patients should be encouraged to drink plenty of water to promote a good flow of urine to prevent urinary stasis. The predominant aims of treatment of urinary tract infection are rapid and effective therapy of urinary tract infection, prevention of recurrence, prevention of antibiotic resistance, and to prevent further increase in resistance.16 A wide range of antimicrobials has been used to treat urinary tract infections. Antimicrobials with proven efficacy are co-trimoxazole, nitrofurantoin, quinolones, and fluoroquinolones. Ampicillin has been found to be less effective because of resistant strains of *E. coli*, *Staphylococcus saprophyticus*, and *Klebsiella* species. Forty percent of patients experience nausea after the administration of nitrofurantoin. Co-trimoxazole has a tendency to cause gastrointestinal upset and rashes. The main drawback of current antibiotic therapies is the emergence and rapid increase of antibiotic resistance.17

In the present study, a polyherbal formulation Cystone syrup is evaluated for its efficacy and safety. The principal herbs of this formulation include *Tribulus terrestris*, *Boerhaavia diffusa*, *Saxifraga ligulata*, *Cyperus rotundus*, *Asparagus racemosus*, *Dolichos biflorus*, *Vetiveria zizanioides*, *Curcuma zedoaria*, and Tribkatu; and powders of Suvarchika, Narasara, Yuvakshara, and Saindhava.

**Aim**

This study was planned to evaluate the clinical efficacy and safety of a polyherbal formulation (Cystone syrup) in the management of chronic urinary tract infection.
Material and Methods

Study design

This was a double-blind, randomized, and placebo-controlled clinical study conducted at Victoria Hospital, Bangalore between September 2010 and April 2010 as per WHO Operational guidance to support clinical trials of herbal product. The study protocol, case report forms, regulatory clearance documents, product-related information, and informed consent form were submitted to the Institutional Ethics Committee and were approved by the same.

Inclusion criteria

Individuals of either sex aged above 18 years suffering from chronic urinary tract infection were included in the study provided they were able to attend the clinic on all the assessment visits, willing to give the informed consent, and willing to comply with the study procedures.

Exclusion criteria

Patients with any complications like severe pain obstruction requiring immediate surgery, marked hydronephrosis or acute renal failure, patients with severe hepatic or cardiac or mental illness, and patients who were not willing to give informed consent were excluded from the study.

Study procedure

At the initial randomization visit, a detailed medical history, with special emphasis on history of urinary symptoms (burning micturition, frequency of micturition, fever, dysuria, and hematuria) was obtained from all the patients. All the patients underwent a thorough systemic examination. Routine blood analysis, urinalysis, and urine culture were done for all the patients. Urine culture was positive in 46 patients in Cystone syrup group and 45 patients in placebo group. Nine patients’ culture did not reveal any organism on entry into the study. Urine culture showed E. coli as the commonest pathogen followed by B. proteus, Klebsiella, and Pseudomonas. All the patients were randomized arbitrarily using random table into either polyherbal group (n = 50) or placebo (n = 50). Each patient received either Cystone syrup or placebo at a dosage of 2 teaspoonsfuls twice a day after meals for 21 days. At each visit, urinary symptoms were evaluated on a visual analogue score ranging from 0 to 10. The outcome of each group was assessed by comparing burning micturition, frequency of micturition, dysuria with mild fever, and effect of study medication on urinary pathogens and pus cells.

All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as “unrelated” (follows a reasonable temporal sequence from the administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they so desired without assigning reasons. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Noncompliance (defined as failure to take <80% of the study procedures).

Inhibition of Uropathogenic Escherichia coli Adherence and Modulation of H2O2-induced Toxicity with Cystone in NRK-52E Cells

Vidyashankar S, et al.


This study was conducted to evaluate the effect of Cystone on the adherence of pathogenic [2-14C]-acetate-labeled Escherichia coli (MTCC-729) to rat proximal renal tubular cells (NRK-52E cells) and also to assess the antioxidant property of Cystone by using hydrogen peroxide (400 μM) as a pro-oxidant in NRK-52E cells. NRK-52E cells were placed in 96-multiwell culture plates at 1×10⁵ cells per well and H2O2, Cystone, and gentamicin cytotoxicities were evaluated. 1×10⁵/mL of NRK-52E cells were incubated with or without noncytotoxic concentration of Cystone and gentamicin, and with same number of [2-14C]-acetate-labeled E.coli in duplicates for 30 minutes at 37°C. After the incubation period, the supernatant was decanted and the cell monolayer was cleansed with phosphate-buffered saline. Then cell lysis was done using 2 mM NaOH and the radioactive counts were recorded. It was concluded from the results of this study that Cystone moderately inhibits the growth of E. coli and significantly inhibits the adherence of E. coli to NRK-52E cells. A significant reduction in cytotoxicity (73.5%) was noted following the co-incubation of NRK-52E cells with H2O2 and 1% Cystone.
the medication) was not regarded as treatment failure, and reasons for noncompliance were noted.

**Primary and secondary endpoints**

The predefined primary efficacy endpoints were the symptomatic relief and prevention of recurrence. The predefined secondary outcome measures were the incidence of adverse effects and patient compliance.

**Follow-up**

Patients underwent the same evaluations after treatment as were performed at baseline at day 7, day 14, and day 21 regardless of their treatment received and outcome.

**Statistical analysis**

Statistical analysis was performed by repeated measures of ANOVA using Friedman test followed by Dunnett’s multiple comparison post hoc test. Clinical parameters of urinary symptoms were expressed as mean ± SD and investigational parameter values are expressed as presence or absence. The minimum level of significance was fixed at P<.05. Statistical analysis was carried out using GraphPad Prism software Version 4.03.

**Results**

Hundred consecutive patients were enrolled into the trial and were randomly divided into 2 groups of 50 each. Mean age (years) was 43.4 ± 10.8 in Cystone syrup group and 42.3 ± 6.5 in placebo group. In the Cystone syrup group, 14 patients were smokers, 12 were alcoholics, and 17 patients were vegetarians. In placebo group, 13 patients were smokers, 15 were alcoholics, and 22 patients were vegetarians. There was no statistical difference between the Cystone syrup and placebo groups (Table 1).

Data of 96 patients were available for analysis. There was a significant reduction in the mean score of burning micturition from 2.85 ± 0.38 at entry to 2.15 ± 0.55, 1.54 ± 0.78, and 0.23 ± 0.18 at the end of day 7, day 14, and day 21 of the treatment in Cystone syrup group with significance of P<.05 at 21 days as compared to “at entry” values. Significant reduction was also observed in dysuria with mild fever symptoms from 3.01 ± 0.40 at entry to 2.84 ± 0.70, 1.90 ± 0.34, and 1.19 ± 0.42 at the end of day 7, day 14, and day 21 of treatment with Cystone syrup. Patients with symptom of dysuria alone also showed significant improvement (P<.05 at 21 days as compared to “at entry” values). In the placebo group, values were not significantly different statistically compared with the baseline values (Table 2).

In the Cystone syrup group, out of the 46 patients whose urine culture was

**Table 1. Demographic Data of Patients on Entry (n = 100)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cystone syrup</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43.4 ± 10.8</td>
<td>42.3 ± 6.5</td>
</tr>
<tr>
<td>Male:female</td>
<td>18:38</td>
<td>15:35</td>
</tr>
<tr>
<td>Smokers</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Diet (vegetarian)</td>
<td>17</td>
<td>22</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Cystone and Placebo on Urinary Symptoms in Patients with Chronic Urinary Tract Infection**

<table>
<thead>
<tr>
<th>Symptom score</th>
<th>Cystone syrup (n=50)</th>
<th>Placebo (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>Day 7</td>
</tr>
<tr>
<td>Burning micturition</td>
<td>2.85 ± 0.38</td>
<td>2.15 ± 0.55</td>
</tr>
<tr>
<td>Frequency of micturition</td>
<td>2.91 ± 0.30</td>
<td>2.33 ± 0.80</td>
</tr>
<tr>
<td>Dysuria with mild fever</td>
<td>3.01 ± 0.40</td>
<td>2.84 ± 0.70</td>
</tr>
<tr>
<td>Dysuria alone</td>
<td>2.98 ± 0.30</td>
<td>2.53 ± 0.60</td>
</tr>
</tbody>
</table>

*P<.05 as compared to “at entry” values.

**Table 3. Effect of Cystone on Pathogens**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Cystone syrup</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture positive before treatment (n = 50)</td>
<td>Culture negative after treatment (n = 50)</td>
</tr>
<tr>
<td>Ecoli</td>
<td>32</td>
<td>32*</td>
</tr>
<tr>
<td>Bacillus proteus</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sterile</td>
<td>4</td>
<td>44</td>
</tr>
</tbody>
</table>

*P<.01 as compared to “before treatment” value.
positive (before treatment), 32 patients had E coli, 9 patients had B proteus, 4 patients had Klebsiella, and 1 patient had Pseudomonas. In the placebo group, out of the 46 patients whose urine culture positive (before treatment), 30 patients had E coli, 10 patients had B proteus, 4 patients had Klebsiella, and 1 patient had Pseudomonas. At the end of 21 days of treatment, urine of 44 patients became sterile in the Cystone syrup group and urine of only 15 patients became sterile in placebo group. The entire 32 patients urine culture positive for E coli become sterile in the Cystone syrup with significance of P<0.01 (Table 3).

Urine examination showed occasional (0-1/HPF) to few (<10/HPF) pus cells in all the 100 cases. Among 22 patients who were passing few pus cells at entry in the Cystone syrup group, only 3 were still passing few pus cells after 21 days with significance of P<0.01. Out of 21 patients passing few pus cells at admission, 18 were still passing few pus cells after 21 days in the placebo group (Table 4).

Four patients of the placebo group withdrew from the study due to nonresponse to the treatment. No adverse drug effects were reported during the entire study period.

Discussion

Although antibiotic treatment has been very successful in treating urinary tract infection, antibiotic resistance is rising and recurrent infections are a common problem affecting millions of patients. Cystone, a polyherbal formulation based on ancient ayurvedic system of medicine has been used for many years (>70 years) to treat urinary calculi and urinary tract infection.23 In the present study, a polyherbal formulation Cystone syrup was evaluated for its efficacy and safety.

Studies have shown that T terrestris has antimicrobial and cytotoxic effects.20 B diffusa exhibited a significant spasmyloytic activity in the guinea pig ileum, probably through a direct effect on the smooth muscle.21 C rotundus has proven efficacy in the treatment of dysuria.22

In Ayurveda, A racemosus has been described as a rasayana herb and has been used extensively as an adaptogen to increase the nonspecific resistance of body against a variety of stresses.23 A racemosus showed considerable in vitro antibacterial efficacy against E coli, Shigella dysenteriae, Shigella sonnei, Shigella flexneri, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Pseudomonas putida, Bacillus subtilis, and Staphylococcus aureus.24 C zedoaria was found to have potential antimicrobial activity against S aureus, E coli, Pseudomonasa aeruginosa, Vibrio parahemolyticus, S typhimurium, Bacillus cereus, and V parahemolyticus. C zedoaria showed antimicrobial activities against these organisms.25 The analgesic activity of C zedoaria thizomes was proven in a phytochemical analysis study.26 D biflorus and S ligulata have antibacterial, analgesic, and anti-inflammatory activities.27

The beneficial actions observed in this study in the management of chronic urinary tract infection could be due to the synergistic actions of the potent herbs of polyherbal formulation, Cystone syrup.

Conclusion

Urinary tract infection though not life-threatening, reduces the patient’s quality of life by its clinical manifestation. Currently available treatment options for the management of urinary tract infection have various limitations and associated adverse effects. This study was planned to evaluate the clinical efficacy and safety of Cystone syrup in chronic urinary tract infection.

Present study observed a highly significant reduction in the symptoms of urinary tract infection after treatment with Cystone syrup. Out of the 46 patients in urine culture positive patients in Cystone syrup group, 44 patients urine became sterile after the end of treatment. Of the 50 cases in the Cystone syrup group, 22 were passing few pus cells at admission but only 4 were still passing few pus cells after 21 days of treatment.

The beneficial clinical efficacy of polyherbal formulation (Cystone syrup) in the management of urinary tract infection could be due to the synergistic actions of its potent herbs. Therefore, it may be concluded that Cystone syrup is clinically effective and safe in the management of urinary tract infection.

**Table 4. Effect of Cystone on Pus Cells**

<table>
<thead>
<tr>
<th>Pus cells</th>
<th>Cystone syrup</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0 (n = 50)</td>
<td>Day 21 (n = 50)</td>
</tr>
<tr>
<td>Occasional (0–1/HPF)</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Few (&lt;10/HPF)</td>
<td>22</td>
<td>3*</td>
</tr>
<tr>
<td>More (10–50/HPF)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*P<0.01 as compared to “Day 0” value.
References

Urinary Tract Infection and Its Management by Renalka

Pandey KK, et al.


ABSTRACT

Urinary tract infection (UTI) is a common disorder in all age groups and in both sexes, globally. Many drugs have been introduced for the treatment of UTI but the problem of drug resistance and toxic manifestations of long term use of these drugs are common. Keeping in view these features and the fact that Ayurveda has guidelines to preserve positive health and provide relief from disease, Renalka syrup was evaluated to treat UTI. In this clinical trial, 30 female patients suffering from symptoms of UTI were given Renalka syrup at a dosage of 2 teaspoonfuls BID. Detailed investigations were done on a prescribed proforma and recorded before and after treatment at weekly intervals for a period of 4 weeks. A significant reduction in the clinical symptoms of UTI and common pathogens especially Escherichia coli, Bacillus proteus, Klebsiella, and Pseudomonas proved the efficacy of Renalka in the management of UTI.

Key words: Urinary tract infection, Renalka, E coli, B proteus, Klebsiella, Pseudomonas.

Introduction and Aim

Urinary tract infection (UTI) is a very common disorder among all age groups and affects both sexes. Many efforts have been made for the treatment of UTI but the problem of drug resistance and dependence along with untoward effects of long-term therapy are very common while managing the UTI. In Ayurveda a large number of drugs have been used for the management of UTI, to provide relief from the symptoms, and prevent its recurrence.1,2

The present clinical trial of Renalka syrup in the management of UTI is aimed to evaluate the drug in terms of its efficacy and safety, so that renal functions are maintained within its normal limits.

Materials and Methods

The present clinical trial was carried out in 30 female patients between the age group of 22 to 46 years, attending Prasuti Tantra OPD of SS Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi. A complete clinical history of the patients was recorded in a specially prepared research proforma and patients were registered in the trial with an informed consent for the given treatment. Urine analysis and culture were done in all the cases before starting the clinical trial. Renalka syrup was given twice daily at
a dosage of 2 teaspoonfuls for 4 weeks. Urine analysis was done every week and clinical findings were recorded. Urine culture was analyzed at the end of 4 weeks treatment. The final assessment of results was done at the end of 4 weeks.

It was noted that 26 patients complained of burning micturition, 21 had frequency of urination, 12 patients had severe dysuria with mild-to-moderate fever, and 12 patients complained of only dysuria as a presenting symptoms (Table 1).³

Urine culture was done in all the 30 patients before starting the treatment. The culture was positive in 90% of patients. Out of the 27 patients (90%), 21 patients (70%) were positive for _E coli_, 10% for _B proteus_, 7.4% for _Klebsiella_, and 3.7% for _Pseudomonas_.

Urine analysis revealed the presence of albumin in 20 patients, pus cells in 23 patients, epithelial cells in 19 patients, and red blood cells in 5 patients.

During the course of treatment no untoward effects of the drug were observed. On completion of treatment, no drug dependency and side effects were observed. Hence, Renalka was found to be safe with no side effects or drug dependency.

### Results

The response to Renalka syrup was recorded after every 7 days. There was marked relief in burning micturition (96.15%) and frequency of micturition (95.23%). All patients showed complete relief from dysuria. Thus, Renalka syrup was clinically effective in relieving symptoms and controlling infection.

It is obvious from the table that with the treatment of Renalka for 4 weeks at a dose of 2 tablespoonfuls, twice daily, the causative pathogens _B proteus_, _Klebsiella_, and _Pseudomonas_ were completely eliminated. Urine cultures of 19 out of 21 cases showed negative result for _E coli_ (Table 2).

### Discussion

The clinical trial of Renalka, an Ayurvedic preparation, has proven its efficacy and safety in chronic UTI. The trial drug Renalka syrup has been quite effective in controlling and relieving clinical symptoms significantly. The present study also observed the following:

- Bactericidal effect against pathogens such as _E coli_, _B proteus_, and _Klebsiella_
- Significant relief from associated symptoms
- Beneficial response of drug within 1 week of treatment
- No untoward effects during the course of treatment

### References


---

### Table 1. Clinical Response After 4-week Treatment

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of patients</th>
<th>Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning micturition</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Frequency of micturition</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Dysuria with mild fever</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Dysuria alone</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 2. Effect of Renalka on the Pathogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>Culture positive before treatment</th>
<th>Culture negative after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E coli</em></td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td><em>B proteus</em></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Urinary Tract Infection in Postmenopausal Women

Raz R.


**ABSTRACT**

Urinary tract infection (UTI) is the most common bacterial infection in women, in general and in postmenopausal women, in particular. Two groups of elderly women with recurrent UTI should be differentiated regarding age and general status: healthy, young postmenopausal women aged 50 to 70 years who are neither institutionalized or catheterized and elderly institutionalized women with or without a catheter. Bacteriuria occurs more often in elderly functionally impaired women, but in general it is asymptomatic. However, the risk factors associated with recurrent UTI in elderly women are not widely described. In a multivariate analysis, it was found that urinary incontinence, a history of UTI before menopause, and nonsecretor status were strongly associated with recurrent UTI in young postmenopausal women. Another study described the incidence and risk factors of acute cystitis among nondiabetic and diabetic postmenopausal women. Independent predictors of infection included insulin-treated patients and a lifetime history of urinary infection. Another important factor in postmenopausal women is the potential role that estrogen deficiency plays in the development of bacteriuria. There are at least two studies showing a beneficial effect of estrogen in the management of recurrent bacteriuria in elderly women. One of these studies showed that vaginal estrogen cream reduced vaginal pH from 5.5 ± 0.7 to 3.6 ± 1.0, restored lactobacillus, and decreased new episodes of UTI. Another study reported similar results using an estriol vaginal ring. However, contradictory results are found in the literature. New strategies have been researched for reducing the use of antibiotics in the prevention and treatment of UTI.

**Key words:** Bacteriuria, elderly women, postmenopausal women, urinary tract infection

**Introduction**

Urinary tract infection (UTI) is the most common bacterial infection in young and elderly women. Despite the higher incidence of bacteriuria in elderly women, most UTI research has been conducted in young women. This study will discuss epidemiological studies regarding risk factors associated with bacteriuria in elderly women. Bacteriuria in the elderly is associated with high mortality rates; however, in most cases, bacteriuria is asymptomatic and not a causal factor of death.

Estrogen deficiency plays an important role in the development of bacteriuria. Several studies have been conducted showing the efficacy of estrogen (orally and vaginally) in the prevention of UTI. Yet, the literature is divided on this subject, and other studies have not shown any advantage in using estrogen.

This study will focus on the updated known data regarding the use of estrogen in the prevention of bacteriuria in elderly women. The alarming increase in multidrug-resistant uropathogens makes it imperative that alternative strategies are found. One strategy is the restoration of flora with lactobacilli using probiotics and another is the use of cranberry, a competitive compound that inhibits the attachment of bacteria to the uroepithelial mucosa, and thereby reduces the frequency of UTI.
Methodology
A systematic literature search was performed of studies conducted over the past 15 years. A few recent studies have investigated the management of UTI in postmenopausal women. The data were collected from the most up-to-date published studies and guidelines, which were found by searching Medline, PubMed, and the Cochrane database with the following key words: “bacteriuria in elderly women” and “postmenopausal women and UTI”. A total of 190 papers were screened by title and abstract: 111 for the first keyword and 79 for the second. Only English publications addressing the keywords were screened. The 25 references used in the text were assessed according to the level of scientific evidence involved. The studies were rated according to the level of evidence (LoE) and the grade of recommendations (GoR) by using The International Consultation of Urological Diseases (ICUD) standards.

Demography
UTI is the most common bacterial infection in women. Three groups of women with recurrent UTI should be distinguished on the basis of age: premenopausal women, healthy postmenopausal women between the ages of 50 and 70 years who are neither institutionalized nor catheterized, and elderly institutionalized women, who are in many cases catheterized.

Bacteriuria occurs more often in functionally impaired women than in those who are not impaired; persistent bacteriuria is seen more often in nursing home residents, and transient bacteriuria is seen more often in young, healthy postmenopausal women. The majority of elderly women with bacteriuria is asymptomatic and should not be treated with antibiotics (LoE 1b). In young to middle-aged women, the prevalence of UTI is <5%, rising considerably with advancing age. Epidemiologic studies have shown that 15% to 20% of 65 to 70-year-old women have bacteriuria, compared with 20% to 50% of women >80 years old.

Despite the high incidence of bacteriuria in postmenopausal women (young and institutionalized), most UTI research has been conducted in younger women. Hence, the most common UTI risk factors among healthy younger women, such as frequent vaginal intercourse, spermicide use, diaphragm use, condom use, a previous UTI history, recent antibiotic use, and nonsecretor status, were not widely investigated in middle-aged and elderly women (LoE 2a).

Bacteriuria in young vs elderly women
Foxman, et al conducted a case-control study investigating the role of health behavior and sexual and medical history in UTI risk among otherwise healthy women aged 40 to 65 years. They showed that sexual activity was not associated with acquiring UTI in this age group, whereas a history of UTI during the past year, urine loss, antibiotic use during the previous 2 weeks, and exposure to cold during the previous 2 weeks were positively associated with UTI. In addition, drinking cranberry juice and taking vitamin C were moderately protective (LoE 2b).

Risk Factors
A case-control study compared 149 postmenopausal women with a history of recurrent UTI with 53 age-matched women with no history of UTI. They looked for risk factors in healthy noninstitutionalized and noncatheterized women.

Three urological factors, namely, incontinence (41% of case patients vs 9% control patients; P<.001), presence of a cystocele (19% vs 0%; P<.001), and postvoiding residual volume (28% vs 2%; P<0.00008) were strongly associated with recurrent UTI. Multivariate analysis showed that urinary incontinence (odds ratio [OR], 5.79; 95% confidence interval [CI], 2.05–16.42; P=0.0009), a history of UTI before menopause (OR, 4.85; 95% CI, 1.7–13.84; P<0.003), and nonsecretor status (OR, 2.9; 95% CI, 1.28–6.25; P = 0.005) were most strongly associated with recurrent UTI in postmenopausal women (LoE 2a).

Jackson, et al described the incidence and risk factors for acute cystitis among nondiabetic and diabetic postmenopausal women and the possible effect of estrogens on those women (LoE 2a). During 1773 person-years of follow-up, 138 symptomatic UTIs occurred (incidence, 0.07 person-year). Independent prediction of infection included insulin-dependent diabetes mellitus (hazard ratio 95% CI, 1.7–7.0) and a lifetime history of UTI (hazard ratio for 6 or more infections, 6.9; 95% CI, 3.5–13.6). However, a borderline association included a history of vaginal estrogen cream use in recent months (hazard ratio, 1.8; 95% CI, 1.0–3.4), and a history of kidney stones (hazard ratio, 1.95; 95% CI, 0.9–3.5). However, sexual activity, urinary incontinence, parity, postcoital urination, vaginal dryness, use of cranberry juice, vaginal bacterial flora, and postvoid residual bladder volume were not associated with the incidence of acute cystitis after multivariable adjustment.
A study by Moore, et al found that recent sexual intercourse, as described for younger women, was also strongly associated with incident UTI in other healthy postmenopausal women (LoE 2b). In the older, institutionalized women, urine catheterization and functional status deterioration appeared to be the most important risk factors associated with UTI (LoE 2a). The risk of UTI increases dramatically with catheterization. Table 1 describes the major factors predisposing adult women to UTI as related to age.

**Bacteriuria and mortality**

Bacteriuria has been discovered as a cause of increased mortality in elderly individuals. Studies of Greek, Finnish, and American patients showed decreased longevity associated with UTI (LoE 1b). The elderly patients with UTI were suffering from a variety of diseases other than UTI that might have increased their susceptibility to infections as well as their mortality.

Nordestam, et al studied a population of elderly patients and compared their longevity in relation to bacteriuria (LoE 1b). There was no increase in mortality related to bacteriuria for otherwise healthy individuals. Bacteriuria per se did not appear to be a risk factor for mortality. In patients with concomitant disease, bacteriuria was associated with increased mortality, but it is not the cause.

**The role of estrogen**

Another important factor in postmenopausal women is the potential role that estrogen deficiency plays in the development of bacteriuria. Postmenopausal women frequently present with genitourinary symptoms; half have genitourinary disorders, and 29% have urinary incontinence (LoE 1b). Postmenopause is characterized by a significant reduction in ovary estrogen secretion, which is often associated with vaginal atrophy. Clinically, it manifests as a syndrome characterized by vaginal dryness, itching, dyspareunia, and urinary incontinence. This may sometimes imitate a UTI (LoE 2a).

Estrogen stimulates the proliferation of lactobacillus in the vaginal epithelium, reduces pH, and avoids vaginal colonization of Enterobacteriaceae, which are the main pathogens of the urinary tract. Figure 1 describes the relationship between estrogen and the vaginal flora and the pathophysiology of urinary tract infections in elderly women (LoE 1a). In addition, the absence of estrogen decreases the volume of the vaginal muscles, resulting in slackness of the ligaments holding the ureteric pelvic floor and the bladder, resulting in the development of prolapse of the internal genitalia. Kicovic, et al showed that vaginal cream decreased urogenital complaints associated with atrophic vaginitis (LoE 1b).

A previous randomized, double-blind, placebo-controlled study demonstrated that vaginal estriol treatment had a dramatic effect on recurrent UTIs in postmenopausal women. The results showed that the incidence of UTI in women who received vaginal estriol was reduced to

<table>
<thead>
<tr>
<th>Table 1. Major Factors Predisposing Adult Women to UTI as Related to Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (year)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>15–50</td>
</tr>
<tr>
<td>50–70</td>
</tr>
<tr>
<td>&gt;70</td>
</tr>
</tbody>
</table>

![Figure 1. Relationship between estrogen and vaginal flora and pathophysiology of urinary tract infections in elderly women](image-url)
0.5 episodes per year compared with 5.9 episodes per year in women who received placebo. In addition, after 1 month of treatment, lactobacillus appeared in 60% of the estrogen-treated group but in none of the placebo group, and the vaginal pH decreased from 5.5 ± 0.7 before treatment to 3.6 ± 1.0 after treatment (LoE 1a).

Several years later, similar results were obtained by Eriksen, using an estradiol-vaginal ring (LoE 1b). In that study, the women in the estradiol group had a significant reduction in the frequency of urogenital symptoms, such as vaginal dryness, dyspareunia, and urge and stress incontinence after 36 weeks of study. In addition, 45% of the women receiving estradiol were still free of UTI, in contrast with only 20% of the women treated with placebo.

However, contradicting results are found in the literature. For example, another study showed that the use of estriol-containing vaginal pessaries was less effective than the use of oral nitrofurantoin macrocrystals in the prevention of bacteriuria in postmenopausal women. This study also showed the failure of the estriol-containing vaginal pessaries to restore vaginal lactobacilli and to reduce vaginal pH in those women (LoE 1a).

Brown, et al assessed the effects of hormonal therapy on UTI frequency and examined potential risk factors (LoE 3). They used data from the Health and Estrogen/Progesterone Replacement Study, a randomized, blinded trial of the effect of hormone therapy on coronary heart disease events among 2763 postmenopausal women aged 44 to 79 years with coronary diseases. UTI frequency was higher in the group receiving hormone treatment (0.625 mg conjugated estrogen plus 2.5 mg medroxyprogesterone acetate or placebo followed by a mean of 4.1 years), although the difference was not statistically significant. Statistically significant risk factors for UTI in the multivariate analysis included the following: women with diabetes mellitus in treatment (insulin OR, 1.81; 95% CI, 1.4–2.34), oral medication (OR, 1.44; 95% CI, 1.09–1.9), poor health (OR, 1.34; 95% CI, 1.14–1.57), vaginal itching (OR, 1.63; 95% CI, 1.07–2.5), and urge incontinence (OR, 1.51; 95% CI, 1.30–1.75). UTIs in the previous years were strongly associated with a simple UTI (OR, 7.00; 95% CI, 5.91–8.92) as well as with multiple UTIs (OR, 18.51; 95% CI, 14.27–24.02).

Jackson, et al did not see that the use of oral or vaginal estrogen was a protective factor in order to avoid recurrent UTI (LoE 2a).

In conclusion, the efficacy of estrogen in the prevention of UTI in postmenopausal women with recurrent infections remains questionable. From a clinical perspective, the main currently recommended use of estrogen (probably vaginal and not oral) is in postmenopausal women, especially those infected with multidrug-resistant uropathogens, which limits the options and effectiveness of antimicrobial prophylaxis, and in women in whom the symptoms are related to atrophic vaginitis. Table 2 summarizes the indications and contraindications for estrogen therapy in UTI.

### Table 2. Indications and Contradictions for Estrogen Therapy in UTI

<table>
<thead>
<tr>
<th>Indications</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral therapy</td>
<td>Avoid menopausal symptoms</td>
</tr>
<tr>
<td>Vaginal therapy</td>
<td>Prevent osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Prevent ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td>Prevent UTI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td></td>
<td>High blood pressure</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Thromboembolic disorders</td>
</tr>
<tr>
<td></td>
<td>Gallstones</td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
</tr>
</tbody>
</table>

### Difficulties in vaginal therapy

| Physical limitations | Tremor, obesity, status after cerebrovascular accident, dementia, psychological problems, education/cultural behavior. |

---

**Treatment**

Treatment of acute cystitis and pyelonephritis in otherwise healthy postmenopausal women is similar to that in premenopausal women; however, short-term therapy in...
postmenopausal women is not as well documented by controlled studies as in younger women. Raz and Rozenfeld published a study in postmenopausal women (mean age 65 years) with uncomplicated UTI in which ciprofloxacin, 200 mg once daily for 3 days (LoE 1b), was significantly more effective in both short- and long-term follow-up than a 7-day course of cephalexin, 500 mg 4 times daily, even though all the uropathogens were susceptible to the two agents. In another double-blind study (LoE 1b), including a total of 183 postmenopausal women of at least 65 years of age with acute uncomplicated UTI, similar results were obtained with either a 3-day or a 7-day oral course of ciprofloxacin 250 mg 2 times daily (bacterial eradication 2 days after treatment 98% vs 93%, P = .16), but the shorter course was better tolerated. The rate of bacterial eradication in this study was generally high, and the rate of bacterial resistance to ciprofloxacin low (GoR A).

Asymptomatic bacteriuria in elderly women should not be treated with antibiotics (GoR A).

The optimal antimicrobials, dosages, and duration of treatment in elderly women appeared to be similar to those recommended for young postmenopausal women (GoR C). However, these results should not be extended to the frail elderly geriatric population with significant comorbidities, who frequently present with UTI caused by more resistant Gram-negative organisms and in whom treatment duration should be prolonged as in complicated UTI.

Estrogen (especially vaginal) could be administered for prevention of UTI; yet, the results are conflicting (GoR C). There are at least two clinical studies showing that vaginal estriol and estradiol-releasing vaginal rings restore vaginal flora, reduce pH, and reduce the number of symptomatic bacteriuria. However, it appears that oral estrogen does not reduce the incidence of UTI in postmenopausal women.

Alternative methods, like cranberry and probiotic lactobacilli, can contribute to preventing recurrent UTI in postmenopausal women, but more well-conducted studies are required to define their exact role and efficiency (GoR C). Once complicating factors, such as urinary obstruction, neurogenic bladder disturbances, etc., can be ruled out, an antimicrobial prophylaxis should be carried out as recommended for premenopausal women (GoR C).

New strategies
The alarming increase in multidrug-resistant uropathogens makes it imperative that alternative strategies are found. One strategy is the restoration of the normal flora with lactobacilli using probiotics. Another option is the use of a competitive compound that inhibits attachment of bacteria to the uroepithelium. Unfortunately, both methods have been evaluated without conclusive results, although there is some evidence that probiotics and cranberry are useful in preventing UTI.

Reid, et al demonstrated the possibility of preventing uropathogen infection by using lactobacillus in vitro. Several clinical studies showed that L rhamnosus Gr-1 and L fermentum-RC can colonize the vagina, the first step in preventing bacteriuria (LoE 2a). However, more studies, especially clinical studies, should be carried out to determine the role of probiotics in the prevention of UTI.

Another possibility is the use of cranberry. Cranberries contain a proanthocyanidin that can prevent the colonization of the E coli uropathogen in the vaginal mucosa and reduce the frequency of bacteriuria (GoR C). McMurdo, et al carried out a randomized controlled trial in elderly women to compare the efficacy in preventing UTI of cranberry capsules with trimethoprim (GoR C). The time to first recurrence of UTI was not significantly different between groups. In addition, trimethoprim had a very limited advantage over cranberry in the prevention of recurrent UTI in older women but had more adverse effects and withdrawals.

However, few clinical studies have been conducted, although in small and heterogenic populations, an advantage in the use of cranberry juice or other oral preparations in the prevention of bacteriuria has been shown.

In the elderly population, there is only one clinical quasi-randomized study in elderly women with asymptomatic bacteriuria, which showed that bacteriuria and pyuria were significantly reduced in women taking cranberry juice in comparison with women who received placebo (GoR C). Because asymptomatic bacteriuria in the elderly is not treated, however, the clinical significance of this study remains inconclusive.

Further research
Further wide-scale randomized studies are essential to define and establish the exact role of estrogen therapy, probiotics, lactobacilli, and other possible and available methods to reduce the use of antibiotics.
Conclusions

Bacteriuria, particularly asymptomatic bacteriuria, is a very frequent finding in both healthy postmenopausal and institutionalized women. Urological factors, such as urinary incontinence, presence of any grade of cystocele and postvoiding residual volume, together with previous UTI and nonsecretor status, are associated with recurrent UTI in this population. Some studies showed a relationship between bacteriuria with diabetes or sexual intercourse. The role of vaginal or oral estrogen together with the use of probiotics and lactobacilli remains questionable.

Catheter-related Urinary Tract Infection in Patients Suffering From Spinal Cord Injuries


Urinary tract infection (UTI) is common in patients with spinal cord injuries because of incomplete bladder emptying and the use of catheters that can result in the introduction of bacteria into the bladder. A total of 145 patients suffering from spinal cord injuries, admitted to the Institute for Physical Medicine and Rehabilitation, Centre for Paraplegia of the Clinical Centre of the University of Sarajevo, were included. The patients were divided in 3 groups according to the method of bladder drainage: Group A (n = 61) consisted of patients on clean intermittent catheterization; Group B (n = 54) consisted of patients with indwelling catheters; Group C (n = 30) consisted of patients who had performed self-catheterization. From a total of 4539 urine samples, 3963 (87.3%) were positive and 576 (12.7%) were sterile. More than 90% of the infected patients were asymptomatic. The overall rate of urinary infection amounted to about 2.1 episodes, and bacteriuria to 8.1 episodes per patient. 77% of infections (113/145) were acquired within 7 days from catheterization. Infection was usually polymicrobial; the greatest number of urine samples 1770/3943 (44.9%) included more than one bacterium. The vast majority of cases of UTI and bacteriuria are caused by gram-negative bacilli and enterococci, commensal organisms of the bowel and perineum, representative of those from the hospital environment. Providencia stuarti (18.9%) being the most common, followed by Proteus mirabilis (16.3%), Escherichia coli (11.8%), Pseudomonas aeruginosa (10.2%), Klebsiella pneumoniae (8.1%), Morganella morgani (5.4%), Acinetobacter baumannii (4.6%), Providencia rettgeri (3.5%). About 15.7% of isolates were gram-positive with Enterococcus faecalis (8.6%) as the most common. About 55.3% of isolates were multidrug-resistant, and the highest rates of resistance were found among Acinetobacter baumannii (87.8%), Providencia rettgeri (86.7%), Pseudomonas aeruginosa (85.4%), Providencia stuarti (84.3%) and Morganella morgani (81%). Lower rates of resistance were found in Group C, ie, patients on intermittent self-catheterization. Eradication of organisms was achieved in only 53 (10.05%) of patients; hence, antibiotic therapy had no or very low effect. Significant correlations were found between the method of catheterization and the frequency of bacteriuria and UTI. The analysis of Group C showed a rate of lower UTI and bacteriuria than the other two groups of patients.
Epidemiology of Pediatric Urolithiasis

Sharma AP, Filler G.


**Abstract**

Pediatric urolithiasis has increased globally in the last few decades. There has been a change in the pattern of stone composition with an increase in the frequency of kidney stones and a decrease in bladder stones. The role of familial predisposition and environmental factors in pediatric urolithiasis is now better understood. Metabolic factors are more common in pediatric urolithiasis than in adult stone disease. This review updates on the epidemiology of pediatric urolithiasis with a focus on the changing trends in the stone disease, current spectrum of stone disease encountered in clinical practice, individual predisposition, and the role of environmental factors in stone formation.

**Key words:** Urolithiasis, pediatrics, kidney stones, bladder stones, urinary tract infection (UTI)

**Introduction**

Pediatric urolithiasis is an important kidney disorder encountered in clinical practice. There has been considerable regional variability in the reported incidences of urolithiasis. Also, there is a growing body of evidence demonstrating that the overall incidence of pediatric urolithiasis is increasing. A better understanding of different risk factors can help with risk stratification in an individual subject and can guide specific measures to prevent stone recurrence. This review focuses on the current state of knowledge on the prevalence of pediatric urolithiasis, temporal trends in stone disease, and the status of different risk factors in stone formation. The risk factors for urolithiasis include an individual’s susceptibility to form stones, such as genetic predisposition and metabolic abnormalities, and environmental factors that facilitate stone disease, such as dietary practices as well as local climate characteristics.

**Prevalence of Urolithiasis**

Prevalence of urolithiasis varies in different countries. In adults, the prevalence is relatively higher in Western countries than in the Eastern hemisphere. The reported prevalence of urolithiasis increases from 1% to
The regional variability in urolithiasis is multi-factorial and may depend on local conditions and practices. In a nationwide survey from the USA on 1,167,009 adults, the odds of stone-formers. Similar to the regional variability seen in adults, the prevalence of pediatric urolithiasis also varies in different parts of the world. In the USA, urolithiasis is said to be responsible for 1 in 7600 to 1 in 1000 pediatric hospital admissions. In asymptomatic Turkish primary school children, the prevalence of pediatric urolithiasis is reported to be 1%. Urolithiasis contributed to 7% of general outpatient consultations in all children’s hospitals in Venezuela during 1998. In a hospital-based study from Ethiopia, 13% of admissions were due to urolithiasis, and close to half of these admissions were in the age group of 0 to 19 years. The prevalence might be higher than what hospital-based studies suggest, as subjects with asymptomatic stones may be missed. This point was highlighted by a 3.5% prevalence of x-ray-identified calcifications in the upper urinary tract in a cross-sectional study on 3398 randomly selected asymptomatic Scottish adults.

The etiology of regional variability in urolithiasis is multi-factorial and may depend on local conditions and practices. In a nationwide survey from USA on 1,167,009 adults, the odds of stones among participants residing in Southeast USA were nearly double of those living in the Northwest states. The risk of kidney stones in USA increases from the West to East and from the North to South. The region of USA with a higher prevalence of kidney stones has been labeled the “stone belt” (also called the “kidney stone belt”). The term stone belt dates back to at least 1976, and it applies to the region in the Southeast USA that includes Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia and Kentucky. Similar regional variation was observed in an Italian study with a higher stone incidence in Southern Italy compared to the North of Italy. The Afro-Asian stone belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia to Philippines. Within a stone belt, the incidence of urolithiasis varies within the regions due to the local conditions and practices.

**Trends in the Prevalence and Pattern of Urolithiasis**

The epidemiologic studies have shown a progressive increase in the incidence of pediatric urolithiasis over the last few decades, referred to as a “stone wave.” An earlier study from 1951 did not find a single case of urolithiasis in 21,835 children at the Babies Hospital in New York. In later studies from the 1960s and 1970s, urolithiasis in children increased steadily. These studies reported the incidence of pediatric urolithiasis in the range of 1 in 6000, 1 in 7600, and 1 in 1850 hospitalized children. This increase in stone incidence has become more pronounced in recent years. VanDervoort, et al reported a 5-fold increase in the prevalence of pediatric urolithiasis in North American children in the last decade. Similar trends were also observed in other countries. Annual pediatric referrals for urolithiasis in Turkey showed a 5-fold increase in the last decade. It cannot be ruled out that advances in imaging techniques contributed to the reported increase; however, the trend has also paralleled with improved socioeconomic conditions and increased consumption of a protein-rich diet.

Pediatric urolithiasis has also shown a change in the pattern of stone composition and localization. At the beginning of the last century, bladder calculi, composed of ammonium urate were common in Europe; whereas over the past 100 years the pattern has changed to a higher frequency of calculi localized in the upper urinary tract. Moreover, calcium oxalate and calcium phosphate calculi became much more prevalent. This change has been reported from both developed and developing countries. Struvite stones have decreased in frequency and their occurrence has become limited to children with predisposed conditions such as obstructive uropathy and recurrent urinary tract infections. Bladder stones composed of ammonium urate and calcium still remain prevalent in malnourished children and are more commonly reported in developing countries. Nonetheless, the pattern of pediatric urolithiasis in developing countries is now changing, which is similar to trend that was observed in the Western hemisphere over the last century.

**Stone Composition**

Calcium oxalate is the most common stone worldwide, and accounts for 60% to 90% of pediatric urolithiasis. Struvite constitutes 1% to 18% of the stones in developed countries. Calcium phosphate accounts for 10% to 20% stones. Uric acid constitutes 5% to 10%, cystine 1% to 5% (1 in 15000 live births) and mixed or miscellaneous 4% of the pediatric stones. Cystine stones have a higher prevalence in endemic areas and in
communities with high consanguinity. The reported prevalence of uncommon stone types could be an underestimation in many developing countries due to the unavailability of required diagnostic tools.

Metabolic Risk Factors

Pediatric urolithiasis requires a comprehensive metabolic evaluation to identify underlying risk factors. Metabolic risk factors increase the risk of stone recurrence. The prevalence of metabolic risk factors ranged from less than 20% to greater than 50% in different studies. Hypercalciuria and hypocitraturia are the common metabolic abnormalities, detected in one-third of the stone-formers. The prevalence of hyperuricosuria and hyperoxaluria has been reported to be approximately 20%.

Hypercalciuria

Hypercalciuria is defined as a urinary calcium excretion in excess of 0.1 mmol/kg per 24 h or 4 mg/kg per 24 h. Hypercalciuria can be associated with elevated plasma calcium levels, as in primary hyperparathyroidism, or it can occur with normal serum calcium levels. Hypercalciemia-associated hypercalciuria needs further evaluation of the etiology of hypercalcemia. Normocalcemic hypercalciuria can be an isolated trait, referred to as idiopathic hypercalciuria, or it can have an associated abnormality such as renal tubular acidosis. The term idiopathic hypercalciuria was introduced by Albright and colleagues to describe normocalcemic hypercalciuria without an obvious etiology. The defect in idiopathic hypercalciuria can be impaired renal tubular calcium reabsorption (renal hypercalciuria) or enhanced intestinal calcium absorption (absorptive hypercalciuria).

An overlap of the 2 mechanisms can also occur, although a differentiation does not change clinical management or prognosis. Calcium balance is negative in almost half the patients with idiopathic hypercalciuria, which can be associated with a reduced bone mineral density. The pathogenesis of decreased bone mineral density in this condition is thought to be secondary to a combination of genetic factors, low calcium intake, and altered cytokine production. Idiopathic hypercalciuria is treated with a low-salt and high-fluid diet, potassium citrate supplementation, and thiazide diuretics.

Hypocitraturia

Urinary citrate inhibits the crystal precipitation and raises the threshold for stone formation through the formation of chelate complexes with calcium. Hypocitraturia can be idiopathic or can be a manifestation of systemic metabolic acidosis, hypokalemia, or inflammatory bowel disease. Hypocitraturia is treated with potassium citrate supplementation.

Hyperoxaluria

Urinary oxalate is mainly derived from endogenous production of ascorbic acid and glyoxylate metabolism. In normal circumstances, only 10% to 15% of urinary oxalate originates from dietary intake. Food products with high oxalate content include coffee, tea, vegetables such as beans, canned tomatoes, cocoa, and chocolate. The proportion of dietary oxalate increases in gastrointestinal conditions associated with fat malabsorption, inflammatory bowel disease, or bowel resection. These conditions aggravate oxalate absorption either due to increased gut permeability or by decreased calcium availability for oxalate binding. Oxalate-rich or pyridoxine-deficient foods can also induce enteric hyperoxaluria. Hyperoxaluria due to an inborn error of metabolism is labeled as primary hyperoxaluria (oxalosis). Two types of hyperoxaluria are differentiated: Type I and Type II. Type I hyperoxaluria is the more common of the two and it occurs in 1 per 120,000 live births. It is transmitted as an autosomal recessive trait. The genetic mutation leads to the defect in enzyme alanine glyoxylate aminotransferase (AGXT). This enzyme defect leads to an increase in urinary oxalate, glyoxylic acid, and glycolic acid. Type II hyperoxaluria is due to a defect in the D-glycerate dehydrogenase enzyme, and it is associated with an increase in urinary oxalate and L-glycerate levels. Low-oxalate, high-fluid, and high-calcium diet, trial of pyridoxine supplementation and potassium citrate administration in the presence of low urinary citrate levels forms the cornerstone of therapy. Severe cases can require combined liver-kidney transplantation. It is important to note that a low-calcium diet can cause secondary hyperoxaluria.

Urinary tract infection

Urinary tract infection from urease-producing organisms can predispose to infection stones by splitting urea to ammonia and CO₂. Ammonia preconditions to the formation of struvite and carbonate apatite stones in the presence of concomitant alkaline urine. The association of pediatric urolithiasis with urinary tract infections is approximately 25%. In pediatric urolithiasis, the prevalence of genitourinary anatomical abnormalities such as ureteropelvic junction obstruction and vesicoureteric reflux can range at 14% to 30%.
Familial and Inherited Predisposition

First-degree relatives of stone-formers have 2 to 16 times higher risk of developing renal stones when compared with the general population. In a stone-former, the probability of having a relative with stones may be as high as 35% to 65% as compared with a 5% to 20% probability in a non-stone-former. It is important to understand that familial recurrence does not necessarily imply an inherited genetic cause. Shared environmental factors and common dietary habits can contribute to familial predisposition. After controlling for dietary pattern, genetic factors have also been recognized to play a significant role in urolithiasis. The mode of inheritance for the genetic factors is largely considered to be polygenic. Monogenic inheritance has been identified for relatively less common etiologies such as cystinuria, primary hyperoxaluria, and for selected etiologies of hypercalciuria such as Dent’s disease (the association of low molecular weight proteinuria and hypercalciuria), Bartter syndrome Type V, autosomal dominant hypocalcemic hypercalciuria, familial hypomagnesemia with hypercalciuria, and hypercalciuric nephrolithiasis with hypophosphatemia.

Idiopathic hypercalciuria can have a familial predisposition or can occur in a sporadic form. Family history could be positive in up to 65% of patients with hypercalciuric nephrolithiasis. In familial forms, the pattern of transmission is found to be consistent with autosomal dominant inheritance. Familial pattern has been reported for both absorptive hypercalciuria and renal hypercalciuria. In pedigree analyses, genetic defect was mapped to chromosome 1q23.3-234 for human soluble adenylate cyclase gene; chromosome 12q12-q14 for vitamin D receptor [VDR] gene; and to chromosome 9q33.2-q34.2, from which an appropriate candidate gene remains to be identified.

The role of genetic factors in oxalate handling has been the focus of a few studies. Recurrent idiopathic stone-formers have been reported to have a higher prevalence of anomalous erythrocyte transmembrane oxalate flux. In the affected families, the transmission pattern suggested an autosomal monogenetic trait, with complete penetration and a variable expressivity. Hydrochlorothiazide and amiloride have been shown to restore the oxalate flux to normal. The significance of oxalate flux in the clinical management of nephrolithiasis needs further evaluation.

Ethnicity and Gender

Idiopathic stone disease has been reported to be more frequent in white Caucasians than in African-Americans from both adult and pediatric studies. These differences are difficult to explain based simply on ethnicity. Decrease in ethnic disparity with the change in dietary pattern in African-Americans suggests a predominant role of environmental factors in the observed discrepancy. With regard to gender distribution, males were found to be more susceptible for stones in some pediatric studies, an observation not seen in other studies.

Dietary Habits

Epidemiologic studies indicate a major role of diet in the pathogenesis of urolithiasis.

Both malnutrition and obesity increase the risk of urolithiasis. The increase in the stone disease with malnutrition is associated with ammonium-urate stones in the bladder, whereas obesity predisposes to calcium-containing stones localized in the upper urinary tract. In obesity, insulin resistance has been associated with an increase in urinary calcium and decrease in renal tubular acid excretion. Impaired renal tubular acid excretion lowers urinary citrate level and enhances the risk of stone precipitation.

Evidence supports a link between higher dietary animal protein and increase in stone incidence. Protein consumption in children in Europe and North America is 3 to 5 times higher than the recommended intake. The increase in dietary protein has been associated with an increase in calcium oxalate stones and higher localization of stones in the kidneys. Diet low in animal protein but high in cereal shifts the spectrum toward a higher predominance of bladder stones composed of ammonium and urate ions, more commonly seen with malnutrition.

The lithogenic potential of dietary factors is believed to be through different mechanisms. It results from a combination of a higher renal load of lithogenic substances, and a tendency towards their increased precipitation in the kidneys. Animal proteins are rich in sulfur-containing amino acids such as cystine and methionine. Oxidation of sulfur to sulfate generates acid load that aggravates calcium mobilization from bones. High purine content in animal protein increases the uric acid burden. Urine oxalate level also increases with high protein intake. High protein load increases glomerular filtration and facilitates a higher delivery of these substances to the urinary tract. Calcium forms soluble complex with sulfate generated from the oxidation of
sulfur in proteins. Acid load increases calcium mobilization from the bones, and causes hypercalciuria and low urine citrate levels.

Dietary sodium increases the risk of urolithiasis. Salt intake expands intravascular volume, which can increase urinary calcium level, likely by decreasing renal tubular calcium reabsorption. Increase in salt intake can induce mild systemic metabolic acidosis, which can lower urinary citrate levels, and increases the risk of calcium precipitation in kidneys.

On the contrary, potassium-rich foods lower stone formation through a decrease in urinary calcium excretion. High urinary potassium is believed to increase renal tubular phosphate absorption and consequently inhibit 1, 25-dihydroxyvitamin synthesis. Decrease in 1, 25-dihydroxy vitamin slows intestinal calcium absorption. Potassium-rich foods offer the additional advantage of high citrate content thus decreasing the precipitation of urinary calcium.

Considering the key role of calcium in the pathogenesis of urolithiasis, the interaction between dietary calcium and the risk of urolithiasis has been controversial. High calcium concentration in calcium oxalate and calcium phosphate stones makes it sound intuitive that high dietary calcium will increase urinary calcium levels and the risk of calcium stones. On the other hand, a low-calcium diet can increase intestinal oxalate absorption and enhance the risk of calcium oxalate stones. This important question was addressed in a prospective study on 45,619 men, aged 40 to 75 years, with no history of kidney stones. The risk of urolithiasis was found to be inversely related to dietary calcium intake. With this evidence, dietary calcium restriction is no longer recommended.

The implication of dietary calcium becomes even more significant in children, due to the importance of adequate calcium intake for growth and bone metabolism in the pediatric age group.

A carbohydrate-rich diet has been associated with an increase in urolithiasis in predisposed subjects. Glucose load can induce hypercalciuria, which is ascribed to decreased distal tubular calcium absorption and augmented intestinal calcium uptake. High glucose can also increase the risk of urolithiasis through an increase in urinary oxalate levels.

Climate and Season

Parry and Lister were the first to propose that exposure to sunlight might influence stone formation after they observed an increase in urinary calcium among soldiers during summer but not in winter months. In a large voluntary reported survey on 1,185,124 adults aged 30 years or older, ambient temperature and sunlight exposure was positively associated with stone prevalence after adjusting for other relevant variables. Incidence of urinary stones tends to be higher in countries with warm or hot climates. Even within North America, the prevalence of stones becomes higher with an increase in average annual temperature (5.2°C in North Dakota to 22°C in Florida) and sunlight index (14.6 in Washington State to 39.7 in Florida). In a similar observation from Italy, the highest frequency of urolithiasis was found in Southern Italy and the lowest in Northern Italy. Corresponding to high temperatures, stone recurrence becomes higher in summer and fall than in winter and spring. The peak incidence of stone formation occurs in July, August, and September in the Northern hemisphere.

The relationship between urolithiasis and high ambient temperature can be explained by intravascular volume contraction resulting from a combination of dehydration and inadequate fluid intake. Volume contraction increases urine concentration and promotes stone formation. Higher sunlight exposure can also increase the production of 25-hydroxycholecalciferol in the skin, leading to an increase in 1, 25 dihydroxyvitamin D levels which augment intestinal calcium absorption. Elevated levels of circulating 1, 25 dihydroxyvitamin D have been found in patients with hypercalciuria.

Local Factors Affecting Stone Formation

Local factors have been reported to affect the regional distribution of pediatric urolithiasis.

Intestinal colonization of Oxalobacter formigenes

Deficient intestinal colonization of Oxalobacter formigenes in the North Indian population has been associated with a higher frequency of urolithiasis in the local population. O formigenes is a Gram-negative, anaerobic bacterium that metabolizes oxalate in the intestinal tract and has a prevalence of 46% to 77% in different populations. Deficient intestinal colonization of O formigenes has been associated with increased risk of absorptive hyperoxaluria and calcium oxalate stones.

The reasons for lower colonization of O formigenes in certain populations are not well understood. Recent antibiotic administration and local practices of antibiotic use can affect O formigenes colonization. A study in Ukrainian
children provided early insight into the natural history of \textit{O. formigenes}. This organism was not detected in children younger than 1 year, had a prevalence of 100\% (by polymerase chain reaction; approximately 80\% by culture) between ages 6 and 8, and dropped to approximately 75\% at age 12. Long-term pattern of \textit{O. formigenes} colonization, loss and reacquisition of the bacterium over the course needs evaluation.

The use of \textit{O. formigenes} as a probiotic is at an early stage of investigation. A preliminary trial on 16 patients showed a reduction in urinary or plasma oxalate in 11 patients with no adverse effects; however, none of the patients seemed to be permanently colonized during follow-up.

**Endemic prevalence of distal renal tubular acidosis**

Higher prevalence of renal stones in Northeast Thailand has been attributed to the local endemicity of distal renal tubular acidosis (RTA). Distal RTA induces systemic metabolic acidosis and increases the risk of urolithiasis by inducing hypercalciuria and hypocitraturia. Even in the absence of overt metabolic acidosis, intermittent and mild acidosis from incomplete distal RTA is capable of causing hypercalciuria and renal calculi. In the presence of metabolic acidosis, hypercalciuria results from calcium mobilization from bones during acid buffering. Renal tubular acidification defects can also lower urinary citrate levels. Low urinary citrate concentration facilitates calcium precipitation in the kidneys. Correction of acidosis offers a therapeutic benefit in both complete and incomplete distal RTA.

**Exogenous substances**

Melamine contamination in milk has been recently associated with nephrolithiasis in infants. After initial reports of nephrolithiasis among Chinese infants, attributed to milk-based formula surfaced in the summer of 2008, a systematic search by the Chinese Administration of Quality Supervision, Inspection, and Quarantine (AQSIQ) revealed 22 commercial brands of milk powder with detectable levels of melamine. Melamine 1,3,5-triazine-2,4,6-triamine, or C₃H₆N₆, a synthetic chemical developed in the 1830s, is used in a variety of inedible commercial products including cleaning supplies, dry erase boards, and other plastics and has widespread legitimate uses. Melamine can increase nonprotein nitrogen content and manufacturers add this to milk in order to meet quality control tests for protein-based nitrogen content.

The mechanism of melamine nephrotoxicity is not completely understood, although animal studies have provided some insight. Melamine can precipitate in distal renal tubules and forms intratubular green radial crystals which are distinct from calcium oxalate or calcium phosphate crystals. Renal injury is believed to be secondary to an increase in intrarenal pressure resulting from crystal deposition in distal tubule leading to intratubular obstruction and distal tubular necrosis. Melamine stones are composed of melamine and its metabolite cyanuric acid with uric acid, protein, and phosphate. These stones are not fully radiopaque.

**Conclusion**

The incidence of urolithiasis in children has increased globally over the last few decades. The pattern of stone disease has also changed, with an increase in kidney stones secondary to calcium oxalate or calcium phosphate in the kidneys and a decrease in bladder stones composed of ammonium and urate. Evidence favors a significant role of dietary practices in the increase in pediatric urolithiasis. There are marked regional variations in the stone prevalence that has led to the recognition of “stone belts.” Local climatic conditions play an important role in the stone pathogenesis. Stone occurrence increases in warmer and sunnier regions. The individual risk of stone disease is modified by familial predisposition and genetic susceptibility. Metabolic workup is indicated in all children with a stone disease. Adequate water intake and maintaining a balanced diet are important to reduce the risk of kidney stones. At-risk subjects identified by metabolic workup can benefit by an intervention directed to the specific defect.
Clinical Characteristics and Risk Factors for Septic Shock in Patients Receiving Emergency Drainage for Acute Pyelonephritis with Upper Urinary Tract Calculi

Yamamoto Y, et al.

ABSTRACT

Acute pyelonephritis (APN) is a common complication of ureteral obstruction caused by urolithiasis, and it can be lethal, if it progresses to septic shock. The clinical characteristics of patients undergoing emergency drainage were investigated and risk factors for septic shock assessed. A retrospective study was performed on 98 patients (101 events) requiring emergency drainage for obstructive APN associated with upper urinary tract calculi. Clinical characteristics were summarized, and risk factors for septic shock were assessed by logistic regression analysis. Objective evidence of sepsis was found in 64 (63.4%) events, and 21 events (20.8%) were categorized as septic shock. Ninety-six patients recovered, but 2 patients died of septic shock. This multivariate analysis revealed that age and the presence of paralysis were independent risk factors for septic shock. APN associated with upper urinary tract calculi is a severe disease that should be treated with caution, particularly when risk factors are present.

Key words: Acute pyelonephritis, urolithiasis, septic shock, urinary tract calculi

Background

Acute pyelonephritis (APN) can be broadly divided into uncomplicated and complicated cases. Complicated cases have anatomical or functional abnormality of urinary tract, such as ureteral obstruction caused by urolithiasis. It has been estimated that 41% of patients with complicated APN develop severe sepsis or septic shock. APN associated with upper urinary tract calculi sometimes requires emergency drainage via a ureteral stent or percutaneous nephrostomy. Previous studies on the clinical characteristics of sepsis associated with upper urinary tract calculi have shown that bacteremia is an indicator of severe APN, while old age and poor performance status are risk factors for emergency drainage. Despite intensive management and emergency drainage, the mortality rate remains around 2%. Thus, a retrospective study of the clinical characteristics of patients with septic shock due to APN with upper urinary tract calculi was performed and risk factors for septic shock were investigated.

Methods

A retrospective study was performed on 98 patients (a total of 101 presentations for APN) who required emergency drainage for treatment of APN with upper
Clinical Practice Pearls

urinary tract calculi. The diagnosis of urolithiasis was based on clinical manifestations, urinary sediment, plain x-ray findings, ultrasound, and computed tomography (CT) data. The presence of hydronephrosis and/or renal insufficiency was noted. The diagnosis of acute pyelonephritis was based on clinical manifestations, body temperature, laboratory test results, and imaging data (plain x-ray, ultrasonography, and CT). Emergency drainage was selected, if there was evidence of inflammation, such as high fever (axillary temperature >38°C), a high white blood cell count, and an elevated C-reactive protein (CRP) level. The method of drainage, location and size of calculi, interval from the onset of symptoms to drainage, and duration of hospital stay were analyzed. The white blood cell count, platelet count, serum creatinine, CRP, and serum albumin at presentation were also assessed.

Patients were categorized into groups with or without septic shock and the clinical characteristics of the two groups were compared. Septic shock was defined as severe sepsis plus one of the following: mean blood pressure (BP) <60 mmHg (<80 mmHg for patients with known hypertension) after 40 mL/kg of saline or the need for dopamine (5 mg/kg/min) to maintain a mean BP >60 mmHg (80 mmHg for prior hypertension). Severe sepsis was defined as sepsis associated with at least one of the following signs of organ hypoperfusion or organ dysfunction: abrupt change of mental status; abnormal electroencephalographic findings; platelet count <100,000/mL or evidence of disseminated intravascular coagulation; or cardiac dysfunction on echocardiography.

Univariate analysis was performed with Fisher’s combined probability test or the Mann-Whitney U test. Independent predictors of septic shock were identified by multivariate logistic regression analysis. Variables entered into the model were age, sex, history of urolithiasis, presence of bacteremia, diabetes mellitus, hypertension, and psychosis, history of cerebral infarction (or hemorrhage or aneurysm), cardiovascular disease, presence of paralysis, and performance status (according to the Eastern Cooperative Oncology Group: ECOG). Statistical significance was defined as \( P < .05 \).

Results

Emergency drainage was performed a total of 1, 2, and 3 times in 96 patients, 1 patient, and 1 patient, respectively. All cases had hydronephrosis. Two patients died despite receiving emergency drainage. Table 1 lists the characteristics of the patients and their calculi, as well as intervention and hospitalization data.

Discussion

An obstructed and infected kidney and APN are urological emergencies that sometimes progress to sepsis and/or septic shock. Despite intensive management and emergency drainage, a mortality rate of around 2% may still be expected. Since acute obstructive uropathy due to upper urinary tract calculi raises the renal pelvic pressure and theoretically decreases the uptake of drugs by the kidney, sepsis due to upper urinary tract infection associated with upper tract calculi frequently requires drainage.

It has been reported that patients who are likely to develop sepsis include the elderly, as well as those with diabetes or immunosuppression (transplant recipients, patients receiving chemotherapy or corticosteroids, and patients with acquired immunodeficiency syndrome). A poor performance status, as occurs in patients with spinal cord injury, is a well-known risk factor for renal calculi. Performance status, age, and sex were reported to be independent risk factors for emergency drainage to treat APN with upper urinary tract calculi.

Conclusions

APN due to ureteral obstruction by upper urinary tract calculi can be lethal despite drainage, if it progresses to septic shock. The study has revealed that older age and the presence of paralysis are independent risk factors for septic shock in patients who require emergency drainage. Careful treatment is required for patients with APN and upper urinary tract calculi, particularly those with risk factors for septic shock.
Cardiology

Cardiac Abnormalities in Primary Hyperoxaluria

Mookadam F, et al.


**Background**

In patients with primary hyperoxaluria (PH), oxalate overproduction can result in recurrent urolithiasis and nephrocalcinosis, which in some cases results in a progressive decline in renal function, oxalate retention, and systemic oxalosis involving bone, retina, arterial media, peripheral nerves, skin, and heart. Oxalosis involving the myocardium or conduction system can potentially lead to heart failure and fatal arrhythmias.

**Methods and Results**

A retrospective review of an institution’s database was conducted for all patients with a confirmed diagnosis of PH between 1/1948 and 1/2006 (n = 103). Electrocardiogram (ECG) and echocardiography were used to identify cardiac abnormalities. Ninety-three patients fulfilled the inclusion criteria, 58% were male. Mean follow-up was 11.9 (median 8.8) years. Out of 38 patients who received an ECG or echocardiography, 31 were found to have cardiac abnormalities. Cardiac findings correlated with decline in renal function.

**Conclusion**

The data suggest that physicians caring for patients with PH should pay close attention to cardiac status, especially if renal function is impaired.

Increased 10-year Cardiovascular Disease and Mortality Risk Scores in Asymptomatic Patients with Calcium Oxalate Urolithiasis

Aydin H, et al.


The aim of this study was to document 10-year risk of cardiovascular disease and mortality in asymptomatic patients with urolithiasis. Consecutive 200 patients with calcium oxalate urolithiasis were compared with 200 age- and sex-matched healthy controls. Ten-year cardiovascular disease risk was calculated with the Framingham Risk Score and mortality risk with SCORE risk score. Calcium, oxalate, and citrate excretion were studied as urinary stone risk factors. The results indicate that patients with urolithiasis had higher total cholesterol ($P<.0001$), lower high density lipoprotein (HDL) cholesterol ($P<.0001$), higher systolic blood pressure ($P<.0001$), and high sensitivity C-reactive protein (hsCRP) ($P<.0001$) compared to controls. Patients with urolithiasis had a higher Framingham Risk Scores [OR 8.36 (95% CI: 3.81-18.65), $P = .0001$] and SCORE risk score [OR 3.02 (95% CI: 1.30-7.02), $P = .0006$] compared with controls. The Framingham and SCORE risk score were significantly correlated with urinary calcium ($P = .0001$, $r = .460$, and $P = .005$, $r = .223$, respectively) and oxalate excretion ($P = .0001$, $r = .516$, and $P = .001$, $r = .290$, respectively).

In multiple linear regression analysis, urinary calcium and oxalate excretion, age, sex, total cholesterol, HDL cholesterol, hsCRP, and smoking were the independent predictors of 10-year cardiovascular disease risk and urinary calcium and oxalate excretion, age, sex, total cholesterol, fasting blood glucose for 10-year cardiovascular mortality. In conclusion, patients with calcium oxalate urolithiasis carry higher risk of cardiovascular disease and mortality. All patients should be screened at the initial diagnosis of urolithiasis for the risk factors.
Dermatology

The Relationship Between Infantile Atopic Dermatitis and Urinary Tract Infection

Farajzadeh S, et al.


Atopic dermatitis (AD) is one of the most common infantile diseases. Immunological dysfunctions in AD patients may predispose them to infections. The aim of this study was to evaluate the relationship between infantile AD and urinary tract infection (UTI). In this cross-sectional study, the researchers enrolled 57 patients with AD aged 1 to 24 months that referred to dermatology clinic, and 57 healthy controls who were referred to pediatric clinic. The groups were matched according to age and gender. Urine samples were collected by clean-voided bag method. If a single microorganism was cultured at concentration of \(\geq 10^5\) organisms per millimeter and the existence of white blood cells >10 per microscopic field was seen, the patients underwent suprapubic aspiration. The presence of one organism in suprapubic aspiration sample was regarded as positive culture. Data were analyzed using SPSS version 15 software. \(P\) value of <.05 was considered as the level of significance. Twelve (21.1%) of AD patients and 1 (1.8%) of normal controls had positive urine culture tests. The difference between 2 groups was statistically significant \((P = .001)\). The most common bacteria was \(Escherichia coli\). Infants with AD showed a higher frequency of UTI in this study. So, the study results suggest screening all AD infants for urinary tract infection.

Acute Generalized Exanthematous Pustulosis Associated with Recurrent Urinary Tract Infections

Klein N, et al.

Hautarzt. 2009;60(3):226-228.

Acute generalized exanthematous pustulosis (AGEP) is characterized by sudden onset of nonfollicular aseptic pustules with erythema often accompanied by fever and leucocytosis. While the most frequent cause of AGEP is drug reactions, especially antibiotics, occasional cases have been described as parainfectious. An 82-year-old female presented with recurrent AGEP along with a chronic urinary infection with \(Escherichia coli\). Her cutaneous findings resolved following antibiotic therapy and prophylaxis. To the best of the authors’ knowledge, this is the first case of AGEP associated with an \(E coli\) urinary tract infection.
Urinary Tract Infection as a Risk Factor for Autoimmune Liver Disease: From Bench to Bedside

Smyk DS, et al.


Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis. A variety of environmental and genetic risk factors have been associated with these conditions. Recurrent urinary tract infections (rUTI) have been strongly associated with PBC, and to a lesser extent with AIH. These observations were initially based on the observation of significant bacteriuria in female patients with PBC. Larger epidemiological studies demonstrated that there was indeed a strong correlation between recurrent UTI and PBC. AIH has not been linked to recurrent UTI in epidemiological studies; however treatment of UTI with nitrofurantoin can induce AIH. As Escherichia coli is the most prevalent organism isolated in women with UTI, it has been suggested that molecular mimicry between microbial and human PDC-E2 (the main autoantigenic target in PBC) epitopes may explain the link between UTI and PBC. Multiple studies have demonstrated molecular mimicry and immunological cross-reactivity involving microbial and self-antigen mimics.

Nephrolithiasis in Patients with Intestinal Diseases

Crillo M, et al.


Intestinal diseases may cause the formation of urinary stones through changes in the metabolism of oxalate, calcium, and uric acid. The oxalate that is excreted into urine comes from the catabolism of ascorbic acid and some amino acids or from intestinal absorption of food oxalate. Calcium is absorbed by the gut after the stimulation of active vitamin D and is excreted by the kidney under the control of bone/parathyroid hormone axis. Uric acid, generated by the oxidation of exogenous and endogenous purine bases, is excreted by the kidney through glomerular filtration/tubular secretion, and is soluble in alkaline urine. Several data indicate that patients with inflammatory bowel diseases are at high risk of developing urinary stones containing calcium-oxalate salt or uric acid. Calcium-oxalate stones are caused by colonic oxalate hyperabsorption (secondary to intestinal dysfunction) or by parenteral nutrition. Uric acid stones are typical of patients with severe diarrhea and/or intestinal neostomy, that is, in patients with hyperconcentrated acidic urine. Relationships between malabsorptive intestinal diseases and urinary stones are less well-defined. Preventive countermeasures are not the same for all disorders. Hyperoxaluria should be controlled by diets with a low content of lipids and oxalate but supplemented with calcium and probiotics. The presence of hyperconcentrated acidic urine should be controlled by correct hydration and administration of citrate.
Gynecology

Stone Formation and Pregnancy: Pathophysiological Insights Gained From Morphoconstitutional Stone Analysis

Meria P, et al.


This study was conducted to examine whether stone composition in pregnant women reflects peculiar pathophysiological conditions. The researchers analyzed in detail the composition of stones from 244 pregnant women 17 to 44 years old and from 5712 nonpregnant women in the same age range, as recorded between January 1991 and December 2007. Clinical features were also recorded. All stones were analyzed by morphological examination coupled with infrared spectroscopy. The 2 patient groups were compared by clinical and biochemical characteristics.

Stone episodes in pregnant women manifested mainly in trimesters 2 and 3 (39% and 46%, respectively). Spontaneous passage was noted in 81% of pregnant vs 47% of nonpregnant women (*P*<.0001). Calcium phosphate, mainly in the form of carboxapatite, was the main stone component in 65.6% of pregnant vs 31.4% of nonpregnant women (*P*<.0001). Octacalcium phosphate pentahydrate, a transition phase in calcium phosphate stone formation, was found in a 5-fold higher proportion in carboxapatite stones in pregnant than in nonpregnant women, a finding also suggesting recent stone formation during pregnancy.

The composition of stones manifesting during pregnancy clearly differs from that of stones formed in nonpregnant women of childbearing age, suggesting a different pathophysiology specific to the pregnant state. In view of the pH dependency of calcium phosphate stones, factors that increase the physiological elevation in maternal urinary calcium excretion and pH are likely to have a role in the preferential formation of calcium phosphate stones during pregnancy.

Nephrolithiasis During Pregnancy: Characteristics, Complications, and Pregnancy Outcome

Rosenberg E, et al.


The aim of this study was to evaluate obstetric complications and birth outcome in pregnant women with nephrolithiasis.

A retrospective population-based study comparing all pregnancies of women with and without nephrolithiasis between 1989 and 2010 was conducted. Clinical characteristics were compared, and the obstetric risk factors and labor complication were analyzed.

During the study period, there were 219,656 deliveries, of which 195 women with nephrolithiasis were identified. Nephrolithiasis in pregnant women was significantly associated with recurrent abortions, mild preeclampsia, chronic hypertension, gestational diabetes mellitus, and cesarean deliveries. Nephrolithiasis was also significantly associated with urinary tract infections, pyelonephritis, hydronephrosis, and hydroureret. Nevertheless, no higher rates of premature rupture of membranes, preterm deliveries, or adverse perinatal outcomes (birth weight, Apgar scores, or perinatal mortality) were noted in patients with nephrolithiasis. Using a multiple logistic regression model, obesity (OR 4.4, 95% CI 2.1–9.0) and hypertensive disorders (OR 2.8, 95% CI 1.9–4.1) were independently associated with nephrolithiasis.

Maternal kidney stones are significantly associated with several pregnancy complications, including recurrent abortions, hypertensive disorders, gestational diabetes, and cesarean deliveries. Nevertheless, it is not associated with adverse perinatal outcomes. These findings raise the question regarding the proper management of small asymptomatic kidney stone in a pregnant woman.
Hepatology

Subcapsular Hepatic Hematoma with Right Hepatic Vein Thrombosis: A Complication of Shock Wave Lithotripsy

Gordetsky J, et al.

Extracorporeal shock wave lithotripsy (ESWL) is a well-established, safe, and effective therapeutic modality for surgical treatment of urolithiasis. Hematoma is a rare complication of ESWL and, when it occurs, typically involves the kidney. This study reports the case of a 71-year-old woman who developed severe, persistent abdominal pain after ESWL for a 9-mm stone at the ureteropelvic junction. Posttreatment computerized tomography (CT) scan demonstrated a 13 × 6 cm subcapsular hepatic hematoma. A follow-up CT scan showed expansion of the hematoma and development of hepatic vein thrombosis. This finding, along with persistent abdominal pain and rising liver transaminases, led to surgical intervention. The symptoms of the patient resolved and liver function returned to baseline following liver decompression.

An Increased Risk of Urinary Tract Infection Precedes Development of Primary Biliary Cirrhosis

Varyani FK, et al.

Primary biliary cirrhosis (PBC) is known to be associated with urinary tract infections (UTIs), but whether these precede or follow the liver disease is unclear. The researchers have therefore attempted to determine whether UTIs are more common in people with PBC prior to their diagnosis.

The researchers conducted a case control study in the General Practice Research Database. All cases of PBC first recorded at least 1 year after entry to the data set were selected along with up to 10 controls matched for age and sex. A second unmatched control group who had chronic liver diseases but not PBC were chosen. The main exposures studied were the occurrence of urinary tract infections and pyelonephritis, at least 1 to 5 years before diagnosis. They also performed an analysis restricted to those younger than 55 at diagnosis, as they hypothesized the relationship to be stronger in the younger age group.

PBC is associated with UTI prior to diagnosis, OR 1.50 (CI 1.26–1.78), which was similar 5 years prior to diagnosis and after adjusting for smoking. The strongest relationships were observed in pyelonephritis exposures 5 years before diagnosis in cases under 55 years: adjusted OR were 2.60 (1.02–6.63) in comparison with matched general population controls and adjusted OR were 2.45 (1.02–5.59) in the comparison with chronic liver disease controls.

The researchers found that the association between urosepsis and PBC is specific to this disease and precedes the diagnosis of PBC in a manner not previously observed in human data. This is consistent with a causal relationship.
Infections

Urinary Tract Infections in the Neonatal Intensive Care Unit: Clinical Analysis of 229 Cases

Han YJ, et al.

Objective
To study the clinical features, distribution of pathogens, drug susceptibility, and treatment effectiveness in neonates with urinary tract infection (UTI) and admitted to the neonatal intensive care unit (NICU).

Methods
The clinical data of 229 neonates who developed UTI during their stay in the NICU were retrospectively studied.

Results
The main clinical manifestations of these children included fever/irregular body temperature, refusing to milk feeding, jaundice, vomiting, diarrhea, poor weight gain, and lethargy. The top three pathogens were Escherichia coli, Enterococcus feces, and Klebsiella pneumoniae. E coli and K pneumoniae were highly resistant to ampicillin and most cephalosporins (>85%), and were highly sensitive to imipenem (100%), meropenem (100%), cefoperazone/sulbactam, and piperacillin/tazobactam (>90%). E feces were highly resistant to penicillin (100%), rifampicin (84%), and gentamicin (79%), but were sensitive to vancomycin.

Conclusions
The clinical manifestations of neonatal UTI are often atypical and manifested as systemic symptoms. The main pathogenic bacterium is E coli, and the isolation rate of enterococci can also be high. Most pathogenic bacteria are resistant to penicillin and cephalosporins, and therefore decision-making on drug administration must be based on the results of drug sensitivity tests.

Cultivation and Morphology of Nanobacteria in Sera of Patients with Kidney Calculi

Chen L, et al.
Beijing Da Xue Xue Bao. 2010;42(4):443-446.

Objective
To detect, culture, and characterize the nanobacteria (NB) from sera of patients with kidney calculi in the researchers’ department.

Methods
Blood samples of 24 patients with kidney calculi and of 3 healthy volunteers in the researchers’ department were collected for NB culture in this study. The researchers used immunohistochemistry, von kossa staining, scanning electron microscopy (SEM), and transmission electron microscopy (TEM) to investigate the appearance and components of cultural NB.

Results
Twenty-two blood samples out of 24 (91.67%) showed growth of NB, while no NB were detected in volunteers’ blood samples. The infection rate of stone group was obviously higher than that of healthy volunteers. After a 4-week culture period, the light microscope revealed coccoid-shaped NB with a diameter of 100 to 500 nm, which could be identified by immunohistochemistry and von kossa staining. SEM and TEM (negative staining) revealed NB with a hollow interior coated in needle-like apatite crystals. Such nanoparticles could bud-off new ones and therefore appeared like living organisms.

Conclusion
NB can be identified from sera of most patients involved in kidney calculi. It may have intimate relation to the formation of kidney calculi because the infection rate of NB blood samples of stone patients was significantly higher than that of healthy volunteers. Immunohistochemistry, von kossa staining, SEM, and TEM are special methods for identifying NB from different aspects. The appearance and character are important points to distinguish NB from other nanosized particles.
Neurology

Characteristics of Urinary Tract Infections in Different Patient Subpopulations and Depending on the Bladder Emptying System


The aim of this study was to analyze the prevalence and etiology of urinary tract infection (UTI) in patients with neurogenic bladder depending on the bladder emptying system used as compared to a population with no neurological impairment; and also to assess perception of urinary tract infection by patients with neurogenic bladder.

An epidemiological and prospective study was conducted on 283 patients, in whom a total of 283 urethral cultures were performed. Of these, 106 were patients with neurological damage, 28 were from a control group with no neurological impairment, 74 of those were patients admitted to the intensive care unit (ICU) of the hospital, and 75 were those who attended the emergency room for symptoms of acute UTI.

Positive urethral cultures were found in 66% of patients with neurological damage and 25% of control patients. Within the neurological group, patients with the highest rates of positive urethral cultures were those with myelomeningocele (MMC) (81.5%) and spinal cord injuries (71.7%), with a statistically significant difference ($P = .01$).

The microorganism most commonly found in all subgroups was *Escherichia coli*. In the ICU subgroup, the most commonly found microorganism was *E. faecalis*, followed by *E. coli* and *P. aeruginosa*. Sensitivity for perception by neurological patients as an indication of the presence of UTI was 97.2%, as compared to 80% in the control group.

*E. coli* was found in positive urethral cultures from all subgroups, except in the ICU group. The groups with the highest UTI rates were patients with MMC and spinal cord injuries. Sensitivity and specificity for perception by neurological patients as an indication of the presence of UTI was higher in neurological patients than in the nonneurological control group ($P = .0004$, area: 0.643).

Urinary Tract Infections Complicating Stroke: Mechanisms, Consequences, and Possible Solutions

Poisson SN, et al.


Background and Purpose

Hospital-acquired urinary tract infection (UTI) is a common complication in hospitalized patients. Recently, catheter-associated UTI has been identified by the Centers for Medicare and Medicaid Services as a preventable condition, and additional payments to hospitals for its treatment are now declined, increasing the need for prevention of this important complication.

Summary of Review

This article explores in-depth the pathophysiology, risk factors for, and consequences of UTI after stroke and possible methods to reduce its incidence in the stroke population. Patients with stroke are particularly vulnerable to UTI due to increased risk from immunosuppression, bladder dysfunction, and increased Foley catheter use; and the fever and systemic inflammatory response associated with UTI may impair stroke recovery. UTI is associated with poorer neurological outcomes, longer hospital stays, and increased cost of care after stroke. Intervention strategies previously attempted in this and other populations include prophylactic antibiotics, antiseptic-impregnated catheters, and quality improvement interventions to reduce inappropriate catheterization.

Conclusion

Patients with stroke have different risks for, consequences of, and barriers to reducing UTI than other hospitalized patients. Further research is needed to develop an effective approach to decreasing this important complication in the stroke population.
Abstracts

Ophthalmology

**Postoperative *Morganella morganii* Endophthalmitis Associated with Subclinical Urinary Tract Infection**


The researchers report a case of *Morganella morganii* acute endophthalmitis following clear corneal phacoemulsification cataract surgery in which a coincident asymptomatic chronic urinary tract infection (UTI) was detected postoperatively. *M morganii* is a Gram-negative bacillus that inhabits the gastrointestinal tract and is part of the normal fecal flora. It is an opportunistic pathogen usually encountered in postoperative and nosocomial settings, causing urinary tract and wound infections. Chronic UTI may be a risk factor for postoperative endophthalmitis. A dipstick urinalysis before elective cataract surgery in elderly patients with a history of recurrent UTI may be considered.

**Bilateral Endogenous Endophthalmitis After Holmium Laser Lithotripsy**

Hu V, et al.


Endogenous endophthalmitis is a potentially blinding condition that occurs after the spread of organisms to the eye from a focus of infection elsewhere in the body. The holmium laser has gained increasing acceptance as being safe and effective for endoscopic lithotripsy. The researchers report what they believe to be the first time endogenous endophthalmitis has been described as occurring after holmium laser lithotripsy, although it has been reported after extracorporeal shock wave lithotripsy. This study reports the case of a 55-year-old woman who developed infections in both eyes, 2 to 3 weeks after the lithotripsy, with a good response to appropriate antibiotic treatment.

**Candida albicans Endophthalmitis After Extracorporeal Shock Wave Lithotripsy in a Patient with Liver Cirrhosis**

Toshikuni N, et al.


A 69-year-old man was referred to a hospital because of hepatic failure after extracorporeal shock wave lithotripsy. The diagnosis of urinary tract infection and fungemia due to *Candida albicans* associated with decompensated liver cirrhosis and renal failure was made. Bilateral endogenous endophthalmitis developed during hospitalization. Candidemia, endophthalmitis, and hepatorenal failure improved with intensive therapy. After discharge, endophthalmitis of the left eye relapsed and vitrectomy was performed. Clinicians should be aware that fungemia complicated by endophthalmitis can be caused by extracorporeal shock wave lithotripsy. There might be a risk of such complications among patients with liver cirrhosis in an immunocompromised state.
Orthopedics

Reactive Arthritis Following *Streptococcus viridans* Urinary Tract Infection

Chou YS, et al.


**Aim**

The study reports a case with reactive arthritis (ReA) following *Streptococcus viridans* genitourinary infection.

**Design**

Clinical findings and treatment are presented. The 28-year-old man visited the authors’ hospital due to ciliary injection and hypopyon over left eye. On examination, Behcet-mimicking symptoms were observed, such as genital and oral ulcers and arthritis. Furthermore, *S viridans* was found in the urethral discharge culture. Under the impression of ReA, which was triggered by *S viridans*, nonsteroidal anti-inflammatory drug (NSAID) and antibiotics were prescribed. Complete resolution of ocular and systemic symptoms was achieved after 2 months of treatment.

**Conclusion**

*S viridans* is potential microorganism of ReA. Careful survey and prompt treatment is necessary.

Urolithiasis and Osteoporosis: Clinical Relevance and Therapeutic Implications

Bilić-Curcić I, et al.


Several clinical and epidemiological studies revealed increased bone turnover and lower bone mass in patients with urolithiasis. Bone mass loss is particularly evident in idiopathic calcium stone formers. However, pathogenetic mechanisms and factors implicated in bone loss in these patients are still unknown. Dietary calcium restriction, increased intake of salt and animal proteins, and vitamin D-receptor polymorphisms are likely risk factors, while role of inflammatory cytokines, osteopontin, and prostaglandin-mediated bone resorption is yet to be determined. Regarding treatment and prevention, it has been proven that calcium supplements and high calcium diet with the addition of potassium alkali have an important role in prevention and treatment of both, urolithiasis and osteoporosis. Thiazide diuretics reduce hypercalciuria in renal tubules, and in addition promote osteoblast differentiation. Finally, bisphosphonates, a commonly used drugs in treatment of osteoporosis, show the potential to inhibit calcium stone formation, whereas a possible protective effect of antioxidants in bone loss and renal injury needs to be investigated further.
Pediatrics

Elevated Urine Levels of Heparin-binding Protein in Children with Urinary Tract Infection

Kjölvmark C, et al.


Background

Urinary tract infection (UTI) is a common infection diagnosis in children, and efficient diagnosis and treatment are important to avoid serious complications. In this study, the researchers investigated whether urinary levels of neutrophil-derived heparin-binding protein (HBP) can be used as a marker of UTI in children. These results were compared to those of dipstick analysis, interleukin-6 (IL-6) analysis in urine, and bacterial culturing.

Methods

Seventy-eight children aged 0 to 18 years with fever and/or symptoms indicating UTI were enrolled in a prospective consecutive study. Urine samples were cultured and analyzed with dipstick, and concentrations of HBP and IL-6 were measured.

Results

Fifteen patients were classified as having UTI, 30 patients had fever but were diagnosed with a nonurinary tract infection, and 33 patients had neither UTI nor fever. Using a urine HBP (U-HBP) cut-off level of 32 ng/mL, the sensitivity and specificity for detecting UTI were 93.3% and 90.3 %, respectively. Receiver operating characteristic curves demonstrated that U-HBP levels were a higher specificity indicator of UTI than urine white blood cell counts or urine IL-6 levels; they also showed a higher sensitivity than the results of the urine nitrite test. All patients with significant growth of clinically relevant bacteria had elevated U-HBP levels.

Conclusion

The results indicate that rapid analysis of U-HBP can provide helpful guidance in the management of children with suspected UTI.

Study of Urinary Tract Infection and Bacteriuria in Neonatal Sepsis

Samayam P, et al.


Objective

To determine magnitude of urinary tract infection (UTI) in neonatal sepsis and to evaluate bacteriuria as indicator of neonatal urinary tract infection for use in resource limited settings.

Methods

This prospective study of 200 neonates was conducted in NICU of MVJ Medical College and Research Hospital. Two hundred neonates were included in the study. There were 130 term (93 boys, 37 girls) and 70 preterm neonates (47 boys, 23 girls). Early onset sepsis group comprised 109 neonates and late onset sepsis group comprised 91 neonates.

Results

The overall magnitude of UTI was 6%. The urine culture positivity in the early onset sepsis group was 1.83% and in the late onset group was 10.98% (P<.05). Urine culture positivity in proven sepsis was 6.32% and in suspected sepsis group was 5.78%. The sensitivity of bacteriuria in neonatal UTI was 91.6% and specificity was 97.8%.

Conclusions

Magnitude of UTI in neonatal sepsis is 6%, with urine culture positivity in late onset sepsis being much higher than in early onset sepsis. Bacteriuria has good sensitivity and specificity in resource limited settings in detecting septic neonates with UTI.
Health Benefits of Green Tea—A Review

Tea (*Camellia sinensis*), which is usually consumed as green (unfermented), black (fully fermented), or Oolong (partially fermented) tea, is associated with numerous health benefits. The most significant beneficial effects have been reported with the consumption of green tea. Among those health benefits are the risk reduction/prevention of several types of cancer and prevention of cardiovascular diseases. Green tea is also known to possess anti-inflammatory, antiarthritic, antibacterial, antiangiogenic, antioxidative, antiviral, neuroprotective, and cholesterol-lowering effects. The authors of this study researched the available literature to highlight the efficacy, mechanisms of action, and adverse effects of green tea and its constituent catechins.

Green tea has been linked to the prevention of certain types of cancer. The antioxidant, antimutagenic, and anticarcinogenic effects of green tea could offer protection against cancer caused by environmental agents. Several epidemiological studies and clinical trials have shown that green tea may reduce the risk of chronic diseases, particularly hypertension and coronary heart disease. Green tea consumption has also been associated with increased bone mineral density and protection against hip fractures. The authors report that tea catechins can affect iron absorption, particularly in those at risk for iron deficiency. Noting that the catechins’ effects on other ions are not well understood, the authors suggest that they may affect absorption and metabolism of ions because flavonoids interact with various metal ions.

Tea catechins, especially epigallocatechin-3-gallate (EGCG), appear to have antiobesity and antidiabetic effects. Recent data from human studies indicate that the consumption of green tea or green tea extracts may help reduce body weight, mainly body fat, by increasing postprandial thermogenesis and fat oxidation. One cited study of 6 overweight men given 300 mg EGCG daily for 2 days suggests that EGCG alone has the potential to increase fat oxidation in men and may thereby contribute to the antiobesity effects of green tea.

Cited studies in animal models of diabetes reported reductions in serum glucose levels with the administration of green tea polyphenols. In normal rats, green tea catechins reduced plasma triglyceride levels in an oral glucose-tolerance test. Green tea and green tea extracts have been demonstrated to modify glucose metabolism beneficially in experimental models of type 2 diabetes mellitus. A human study reported that green tea promoted glucose metabolism in healthy human volunteers as shown in oral glucose-tolerance tests.

The authors conclude that long-term consumption of tea catechins could be beneficial to high-fat diet-induced obesity and type 2 diabetes and could reduce the risk for coronary disease. Further research should focus on the pharmacological and clinical effects of green tea and its mechanisms of action.

Excerpted from: Henson S. HerbalGram. 87:29.
Clinical Practice Pearls

Herb Profile: Bacopa monnieri

Introduction
Bacopa is a creeping, prostrate, and succulent perennial that grows naturally in moist or wet areas such as the borders of irrigated fields, streams, water channels, and wells. Native to India, Indochina, Sri Lanka, and the Mascarene islands of Mauritius, Reunion, and Rodrigues, this genus—which consists of 56 species—flourishes in tropical and subtropical regions of the world.

Bacopa produces flowers and fruits throughout the growing season. The flowers have 5 white to pale blue or violet petals, with 1 petal larger than the others. Both the leaves and seed capsules are fleshy and smooth. All parts of the plant are used medicinally, either fresh or dried. In the Indian traditional systems of medicine, preparations are made primarily from the whole dried plant (root, stem, leaf, flower, and fruit).

History and Cultural Significance
Bacopa monnieri is commonly known as Brahmi in Ayurvedic medicine, which means “expands consciousness.” Bacopa monnieri is an important ingredient in several Ayurvedic preparations indicated to prevent aging, re-establish youth, prevent disease, promote healthy longevity, and strengthen brain and mind. The entire plant (including root) is used in traditional Indian medicine for a wide array of conditions. In the Ayurvedic system of medicine, B monnieri is indicated for treating skin diseases, fever, edema, anemia, increased frequency and turbidity of urine, and psychological disorders. The herb is also useful for treating constipation, painful urination (dysuria), edema, nervous debility, poor memory, and brain and nervous weaknesses.

The leaves, in particular are used to treat asthenia (lack or loss of strength) and nervous breakdown. Extracts of aerial parts and root of the herb are used to treat acute bronchitis and other cough in children. Both the fresh juice and a paste made of the leaves are applied topically to relieve the pain of inflamed joints, specifically joint pain caused by arthritis.

Modern Research
The primary chemical components in B monnieri are alkaloids (brahmine and herpestine), flavonoids (glucuronyl-7-apigenin, glucuronyl-7-luteolin, luteolin-7-glucoside, and luteolin), and saponins (bacogenins, bacosides, and bacopasides), and bacopasaponins. In addition, the herb contains hersaponin, monnierin, and triterpines (betulinic acid, bacosine, B-sitosterol, stig mastanol, and stigmasterol).

Bacopa monnieri has been found to have adaptogenic, anticancer, antidepressant, antioxidant, astringent, anxiolytic, cardiotoxic, cholinergic (activated, stimulated, or transmitted by choline/acetylcholine), cognitive-enhancing, diuretic, mildly laxative, refrigerant, sedative, and vasoconstrictive properties.

Future Outlook
Of the estimated 960 medicinal plant species that form the source of 1289 botanical raw drugs in trade in India, Bacopa is among the top 117 species whose annual domestic consumption exceeds 100 metric tons (MT). Ranking at number 19 in terms of volume, Indian domestic consumption of Bacopa is estimated at 2548 MT. In terms of trade volume and consumption, annual demand was estimated between 2,000 to 5000 MT in 2008. Most of the commercial supply is harvested from wild populations.

Incidence of Kidney Stones with Topiramate Treatment in Pediatric Patients

Mahmoud AA, et al.

**Purpose**
This study was conducted to assess the incidence of nephrolithiasis in a group of children on topiramate (TPM) therapy for at least 1 year.

**Methods**
In this retrospective observational surveillance study, the researchers reviewed the medical charts of children on TPM for at least 1 year seen at the Pediatric Neurology Department during the period 2005 to 2010 at King Fahad Medical City. Children with a normal baseline ultrasound report were included. Follow-up ultrasound reports after at least 1 year were collected. However, patients with any evidence of chronic illness or medications that may affect the kidney functions in addition to those who are not compliant with the prescribed dose were excluded. Family history of renal stones, symptoms suggestive of urologic disorders, and comorbidities were recorded.

**Key Findings**
Medical charts of 96 children on TPM with a mean age of 6.9 (±3.8) years were reviewed; 52 (54.2%) of the children were males. The follow up ultrasound showed that 5 children (5.2%) had developed kidney stones. The occurrence of kidney stones was found in 4 female patients (80%) versus 1 male (20%) (P > .05).

**Significance**
Long-term use of TPM may result in increased incidence of asymptomatic kidney stones in the pediatric population. Hence, routine baseline and follow up ultrasound of the urinary system should be recommended during the use of TPM in children.

Hemorrhage During Warfarin Therapy Associated with Cotrimoxazole and Other Urinary Tract Anti-infective Agents: A Population-based Study

Fischer HD, et al.
*Arch Intern Med*. 2010;170(7):617-621.

This study examined the risk of upper gastrointestinal (UGI) tract hemorrhage in older patients receiving warfarin in combination with antibiotics commonly used to treat urinary tract infection, with a focus on cotrimoxazole.

This population-based, nested case-control study using health care databases in Ontario, Canada, between April 1, 1997 and March 31, 2007, identified residents 66 years or older who were continuously treated with warfarin. Cases were hospitalized with UGI tract hemorrhage. For each case, the researchers selected sex-matched control subjects up to 10 years of age. They calculated adjusted odds ratios (aORs) for exposure to cotrimoxazole, amoxicillin trihydrate, ampicillin trihydrate, ciprofloxacin hydrochloride, nitrofurantoin, and norfloxacin 14 days before the occurrence of UGI tract hemorrhage.

The researchers identified 1,34,637 patients receiving warfarin, of whom 2151 cases were hospitalized for UGI tract hemorrhage. Cases were almost 4 times more likely than controls to have recently received cotrimoxazole (aOR, 3.84; 95% confidence interval [CI], 2.33–6.33). Treatment with ciprofloxacin was also associated with increased risk (aOR, 1.94; 95% CI, 1.28–2.95), but no significant association was observed with amoxicillin or ampicillin (1.37; 0.92–2.05), nitrofurantoin (1.40; 0.71–2.75), or norfloxacin (0.38; 0.12–1.26). Compared with amoxicillin or ampicillin, cotrimoxazole prescription was associated with an almost 3-fold risk (ratio of ORs, 2.80; 95% CI, 1.48–5.32).

Among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of UGI tract hemorrhage than other commonly used antibiotics. Whenever possible, clinicians should prescribe alternative antibiotics in patients receiving warfarin.
Case Discussion

Renal Stone Associated with Ketogenic Diet in a 5-year-old Girl with Intractable Epilepsy

Choi JN, et al.

Abstract

In this paper, authors report on a 5-year-old girl who developed a renal stone while following ketogenic diet to treat refractory seizure disorder. Three months after initiating the ketogenic diet, she developed severe abdominal pain and vomiting. The spot urine calcium-to-creatinine (Ca/Cr) ratio and 24-hour urine evaluation showed hypercalciuria. Computed tomography (CT) imaging revealed a stone in the right ureteropelvic junction, resulting in hydronephrosis of the right kidney. The renal stone disappeared 5 days after conservative treatment; the patient’s microscopic hematuria resolved concurrently. In light of this case report, the authors recommend regular monitoring of urine Ca/Cr ratio with ultrasonography for further development of renal stones in patients following the ketogenic diet. If these patients exhibit evidence of symptomatic hypercalciuria or crystalluria, liberalization of fluid restriction and urine alkalization using oral potassium citrate should be considered.

Keywords: Renal stone, ketogenic diet, epilepsy

Introduction

The ketogenic diet was introduced by Wilder in 1921 to treat medically intractable childhood epilepsy. Recently published studies have demonstrated the diet’s antiepileptic effects. Several hypotheses have been put forward to explain the mechanism behind its efficacy. Kalapos proposed that ketone bodies might result in reduced neuronal excitability, resulting in a direct anticonvulsant effect. A study by Janigro suggested that the efficacy of the diet may be related to increased availability of β-hydroxybutyrate, a ketone body readily transported through the blood–brain barrier. However, the mechanisms underlying the protective effect of these compounds are not completely understood.

There have been several reports about renal calculi developing in children on the ketogenic diet since the first report more than 30 years ago. The prevalence of renal calculi in people on the ketogenic diet is 3% to 10%, compared with 1 in several thousand in the general population. Chronic acidosis, dehydration, low urine pH, and fat malabsorption all contribute to the formation of uric acid and calcium oxalate stones. In this paper, the authors describe the case of a 5-year-old girl who developed a renal stone after beginning a ketogenic diet to control refractory complex partial seizures.

Case Report

A 5-year-old girl presented with severe abdominal pain, nausea, and vomiting for 1 day. Her past medical history was significant for eyelid fluttering with or without facial paresis, at least 50 to 100 times per day. Complex partial seizures were diagnosed at 4-years-old; therapy included 2 months of antiepileptic drugs such as zonisamide, valproate, vigabatrin, and clonazepam at an outside hospital. Despite this treatment, her seizures did not improve, so she was subsequently referred to the Epilepsy Center of the authors’ hospital. A subtotal right frontal lobectomy preserving the motor cortex was performed 4 months after localizing the epileptogenic focus using a brain magnetic resonance image, single photon emission computed tomography, and positron emission tomography studies. The initial electroencephalogram pattern was focal slowing and a frequent sharp wave discharged from the right frontal area and focal slowing on the centrotemporal areas. Its pattern changed to a rhythmic sharp wave discharged from the right temporal areas after a right subtotal frontal lobectomy. Despite the epileptic surgery, seizure frequency remained at 50 to 100 times per day as well as
similar seizure patterns and intensity. Ten days after surgery, she was started on a 1300 kcal ketogenic diet with a nonlipid to lipid ratio of 4:1. Although seizure frequency decreased 5 times per day, she developed severe abdominal pain, nausea, and vomiting after 3 months.

On physical examination, she had direct tenderness without rebound tenderness in the right lower abdominal quadrant. Her blood pressure was 107/72 mmHg and chest and abdomen x-rays were unremarkable. Laboratory findings showed a white blood cell count of 395 × 10^3/μL, and platelets 395 × 10^3/μL. Serum total protein was 7.0 g/dL, albumin 4.6 g/dL, blood urea nitrogen 7.7 mg/dL, creatinine 0.3 mg/dL, calcium 9.3 mg/dL, uric acid 3.9 mg/dL, sodium 142 mmol/L, potassium 3.9 mmol/L, chloride 102 mmol/L, and total CO2 12 mmol/L. Urinalysis showed a specific gravity of 1.030, pH 5.0, hematuria (3-5/high power field), and 3-plus ketones.

The spot urine calcium-to-creatinine ratio was 1.0 mg/g (reference level: <0.2) and 24-hour urine calcium excretion was 5.9 mg/kg (reference level: <4 mg/kg), suggesting hypercalciiuria. Twenty-four hour uric acid excretion was within normal limits. In order to evaluate acute appendicitis, abdominal CT was initially performed. It revealed a stone in the right ureteropelvic junction, resulting in hydronephrosis.

The patient was treated with aggressive hydration and she spontaneously passed the stone, so the authors could not check the calculus composition. An intravenous pyelogram demonstrated no definite intrinsic abnormalities in the kidneys, ureters, or bladder; renal ultrasonography indicated the complete resolution of previously noted right side abnormalities. After 1 month, a followup ultrasonography showed no abnormal findings. Because seizure frequency increased by over 40 times per day, she received a right frontal lobectomy and cortisectomy of the perinsular and superior temporal gyri, finally attaining seizure-free status.

**Discussion**

The ketogenic diet has been increasingly used by neurologists over the past 20 years for children with medically intractable epilepsy. Recent studies have reported that 23% to 44% of patients show a reduction in seizure frequency of >50%, including 7% to 22% who become seizure-free after 12 months on the classic ketogenic diet. However, side effects have previously been reported in patients following a ketogenic diet. Renal stones are a significant complication of the ketogenic diet. Calculus composition has been reported as uric acid, calcium oxalate, or a mixture of calcium oxalate and calcium phosphate/uric acid.

There are several reasons underlying the elevated risk of developing renal calculi in patients on the ketogenic diet. First, hypercalciuria can develop due to chronic metabolic acidosis. This metabolic acidosis not only decreases calcium reabsorption in the renal tubules, thus increasing urinary calcium excretion, but also increases bone demineralization because bone phosphate acts as an acid buffer. Second, children on a ketogenic diet show hypocitraturia. Citrate normally binds urine calcium, lowering its concentration, acting as an inhibitor of calcium crystallization. Acidosis induces proximal tubules to both increase citrate absorption and decreases its excretion. As a result, acidosis not only reduces urinary citrate excretion but also increases urinary calcium excretion, aggravating renal stone formation. Third, chronic acidosis persistently causes low urinary pH, which facilitates uric acid crystal formation due to lowered uric acid solubility. These crystals can act as a nidus for calcium stone formation. Lastly, dehydration may be the most significant factor in calculus formation in children on the ketogenic diet, primarily because ketosis has been shown to interfere with the normal thirst mechanism.

In light of these complications, fluid liberalization and urine alkalinization using oral potassium citrate should be considered as prophylaxis to prevent renal stone formation in children beginning this diet. Potassium citrate increases urine pH and solubilizes calcium, thereby decreasing the concentration of free calcium available to crystallize. One of the authors has suggested that initial fasting and fluid restriction are not essential to the ketogenic diet. Because an increase in fluid intake does not diminish the efficacy of the ketogenic diet in controlling seizures and blood ketone levels, these preventive measures may be useful in reducing the formation of renal stones.

In conclusion, the ketogenic diet is a risk factor for kidney stones, and hypercalciuria was more common in those with kidney stones. The authors recommend maximizing fluid intake and alkalinizing the urine to prevent the development of renal stones. Regular urinary studies including calcium-to-creatinine ratio and ultrasonography are highly recommended to detect this possible complication in children receiving the ketogenic diet. Any evidence of hematuria, dysuria, or crystalluria should be evaluated with both a renal ultrasonography and a nephrology referral.
Special Feature

Upcoming Events

Event: Medical Ethics & Legal Medicine
Date: July 21 to 28, 2012
Venue: Venice, Italy
For more details, log on to http://www.continuingeducation.net

Event: Australasian Society of Human Genetics 36th Annual Scientific Meeting
Date: July 22 to 25, 2012
Venue: Canberra, Australia
For more details, log on to http://www.hgsaconference.com.au/

Event: 2012 International Conference on Biological and Life Sciences (ICBLS 2012)
Date: July 23 to 24, 2012
Venue: Singapore
For more details, log on to http://www.icbls.org

Event: Improving Pain Management in Primary Care
Date: July 30, 2012 to August 1, 2012
Venue: Anaheim, California

Event: Internal Medicine Update for Primary Care
Date: August 9 to 11, 2012
Venue: Oahu, Hawaii, United States
For more details, log on to http://www.mceconferences.com/conference-detail.php?conf_id=AU%20201029-31

Event: Annual Global Healthcare Conference (GHC 2012)
Date: August 20 to 21, 2012
Venue: Singapore
For more details, log on to http://www.globalhc-conf.org/

Event: Beyond the Placebo: Biomedical, Clinical and Philosophical Aspects of the Placebo Effect
Date: August 23 to 25, 2012
Venue: Ascona, Switzerland
For more details, log on to http://www.ethik.uzh.ch/ibme/veranstaltungen/placebosymposium.html

Event: UICC World Cancer Congress 2012
Date: August 27 to 30, 2012
Venue: Montreal, Québec, Canada
For more details, log on to http://www.worldcancercongress.org

Date: September 1 to 3, 2012
Venue: Chidambaram, Tamil Nadu, India
For more details, log on to http://www.continuingeducation.net

Event: Internal Medicine: Cardiology
Date: September 5 to 15, 2012
Venue: Civitavecchia, Italy
For more details, log on to http://www.continuingeducation.net

Event: Tuberculosis 2012, Biology, Pathogenesis, Intervention strategies
Date: September 11 to 15, 2012
Venue: Paris, France
For more details, log on to http://www.pasteur.fr/infosci/conf/sb/tuberculosis2012/index.html
Nephroscopy with Carbon Dioxide in Combination with Laparoscopy in the Treatment of Urinary Stones


Laparoscopy in combination with nephroscopy is rarely used for the treatment of complex urinary stones or anatomical abnormalities with difficult access stones. During the nephroscopy, in an opened renal pelvis, large amounts of fluid leaks and collects in the peritoneal cavity and can be a drawback. In these cases, the nephroscopy with use of carbon dioxide (CO2) can be an alternative.

In this study, the researchers present their experience with this technique. The researchers performed surgeries using the 3-port transperitoneal technique. Five patients with urolithiasis were included. Three patients had concomitant ureteropelvic junction stenosis, one with stones in ectopic kidney, and the third had a large stone impacted in the proximal ureter. Patients were treated by pyelolithotomy or ureterolithotomy, combined with flexible nephroscopy using CO2 and dismembered pyeloplasty was performed in appropriate cases. A flexible cystoscope was passed through a port and guided laparoscopically through the opening in the renal pelvis. The gas cannula was connected to the irrigation channel of the endoscope to insufflate CO2 and calculi were extracted with a nitinol basket.

Median age was 45 years (24–58). Mean operative time of nephroscopy was 22.4 minutes (range 15–48). Mean intra-operative blood loss was inestimable. There were no complications or conversion. Residual lithiasis requiring ureteroscopy was present in one patient. Flexible nephroscopy using CO2, in combination with laparoscopy, is a feasible and effective technique for the treatment of urinary stones in selected cases to avoid accumulation of fluid in the peritoneal cavity.

A Method for Rapid Detection of Urinary Tract Infections

Olsson C, et al.
Urology. 2012.

Objective

To determine the reliability of a rapid detection method compared with the reference standard streaked agar plate in diagnosing the presence of urinary tract infection (UTI).

Methods

De-identified clean catch urine specimens from 980 office visit patients were processed during a 30-day period. Classic 1 μL and 10 μL streaked agar plates were used in parallel with the new CultureStat Rapid UTI Detection System (CSRUDS). Urine results were evaluated using the CSRUDS at 30 and 90 minutes after collection. A comparative analysis of the subsequent plate results versus the CSRUDS results was achieved for 973 of these samples.

Results

Positive UTI conditions were accurately identified by both CSRUDS and agar streak plate methods. CSRUDS accurately identified UTI negative conditions with 99.3% reliability at 90 minutes. The negative predictive value of CSRUDS was 99.2% at 30 minutes.

Conclusion

Current agar plating for first-round UTI screening has substantial documented problems that can negatively affect an accurate and timely UTI diagnosis. A novel rapid detection system, the CSRUDS provides UTI negative/positive same-day results in ≤90 minutes from the start of test. Such rapidly available results will enable more accurate and timely clinical decisions to be made in the urology office, particularly regarding infection status before urologic instrumentation.
Drug Info

Cystone® (SYRUP)

The natural choice in urinary calculi & UTI

Introduction
Cystone syrup, a phytopharmaceutical formulation, is recommended for comprehensive management of urolithiasis and urinary tract infections (UTI). Cystone syrup expels kidney stones and ureteric stones, and prevents their recurrence. Cystone syrup is safe and effective in the management of pediatric urolithiasis and UTI, and causes significant reduction of associated symptoms.

Composition
Each 5 mL of Cystone syrup contains:

Exts.
- Gokshura (*Tribulus terrestris*) 91 mg
- Punarnava (*Boerhaavia diffusa*) 67 mg
- Pashanabheda (*Saxifraga ligulata*) 53 mg
- Mustaka (*Cyperus rotundus*) 42 mg
- Shatavari (*Asparagus racemosus*) 21 mg
- Kulattha (*Dolichos biflorus*) 21 mg
- Ushira (*Vetiveria zizanioides*) 21 mg
- Trikatu 20 mg
- Karchura (*Curcuma zedoaria*) 14 mg

Pdrs.
- Saindhava 50 mg
- Suvarchika 42.5 mg
- Yavakshara 5 mg
- Narasara 2.5 mg

Clinical Pharmacology

Cystone syrup has antilithiatic and lithotriptic, pH-renormalizing, diuretic, antimicrobial, anti-inflammatory, demulcent, spasmolytic, antioxidant actions along with bioavailability-enhancing property.

The antilithiatic action of Cystone prevents the deposition, accumulation, and supersaturation of calculogenic chemicals in urine. Cystone also controls oxamide absorption from the intestine. Cystone corrects the crystalloid–colloid imbalance. Cystone inhibits calculogenesis by reducing the stone-forming substances like oxalic acid, calcium hydroxyproline, etc. The lithotriptic action of Cystone helps in the dissolution of calculi. Cystone causes disintegration of the calculi and crystals by acting on the mucin, which binds the particles together. Cystone offers diuretic action and flushes small stones from the urinary tract.

The pH-renormalizing action of Cystone provides cooling action in the urinary system and relieves burning micturition. Cystone provides antimicrobial action against common urinary pathogens responsible for recurrent UTI.

The anti-inflammatory action of Cystone helps reduce inflammatory changes in the mucosa of the urinary tract, as seen commonly in UTI. The demulcent action of Cystone soothes and protects the irritated or inflamed internal tissues of the urinary tract. The antioxidant action of Cystone prevents free radical damage to the urinary tract. The antispasmodic and anti-inflammatory actions of Cystone provide relief from associated symptoms of urolithiasis and UTI.

Indications

- For the prophylaxis and treatment of adult and pediatric urolithiasis:
  - Calcium oxalate stones
  - Calcium phosphate stones
  - Uric acid and urate stones
- Crystalluria
- Prevention of postlithotripsy recurrence
- As an adjuvant in:
  - Chronic UTI
  - Nonspecific urethritis including dysuria
  - Burning micturition
  - Hyperuricemia
Dosage

**Children:** ½ to 1 teaspoonful twice daily after meals.

**Adults:** 1 to 2 teaspoonfuls twice daily after meals.

Recommend adequate water for hydration.

A higher dosage may be recommended for more severe and chronic conditions, and for older children.

Adverse Effects

No adverse effects have been reported.

Contraindications

No absolute contraindications.

Special Precautions

It is advisable not to recommend Cystone syrup in complete ureter obstruction.

Drug Interactions

No clinically or biochemically significant drug interactions have been reported.

Presentation

Pilfer-proof bottles of 100 mL and 200 mL.

Pharmacological Actions of Principal Ingredients

1. Antilithiatic and lithotriptic actions:

   *T terrestris, D biflorus,* and *A racemosus* prevent the deposition, accumulation, and supersaturation of calculogenic chemicals in urine.

   Aspartic and glutamic acids, a group of amino acid compounds derived from *B diffusa*, are the possible agents for dissolving calcium oxalate calculi in the kidneys.

   Extracts of *T terrestris* and *S ligulata* show potential inhibitory effect on the growth of urinary type calcium hydrogen phosphate dihydrate (CHPD) crystals, and thus act as lithotriptics.

2. pH-renormalizing action:

   *A racemosus, V zizanioides,* Narasara, and Saindhava provide cooling action in the urinary system and relieve burning micturition by renormalization of urinary pH.

3. Diuretic action:

   Cystone syrup flushes out small stones and gravels due to the potent diuretic actions of *T terrestris, C zedoaria, B diffusa, D biflorus,* and Yavakshara.

4. Antimicrobial action:

   Cystone syrup provides broad antimicrobial action due to the antimicrobial actions of *T terrestris, C zedoaria,* and *A racemosus* against common urinary pathogens responsible for recurrent UTI, which leads to stone formation.

5. Anti-inflammatory action:

   *C rotundus* and *B diffusa* have anti-inflammatory actions that help to reduce inflammatory changes in the mucosa of the urinary tract, as seen commonly in UTI.

6. Demulcent action:

   *A racemosus* has demulcent property due to its high content of mucilage, and hence, soothes and protects the irritated or inflamed internal tissues of the urinary tract.

7. Spasmolytic action:

   Yavakshara, *B diffusa,* and Suvarchika have antispasmodic action, and thus provide great relief in dysuria.

8. Antioxidant action:

   *B diffusa* and *A racemosus* are strong antioxidant agents that prevent free radical damage to the urinary tract.

9. Bioavailability-enhancing property:

   Trikatu, an ayurvedic formulation comprising a 1:1:1 ratio of dried fruits of *P nigrum, P longum,* and dried rhizomes of *Z officinale,* is widely used to enhance the bioavailability of drugs.

   Piperine from *P nigrum* is absorbed rapidly across the intestinal barrier, and acts as an apolar molecule that forms an apolar complex with drugs and solutes. This modulates membrane dynamics due to its easy partitioning, thus helping in efficient permeability across the barriers, and these membrane modulations help in better bioavailability of nutrients and medications.
Introduction

Cystone tablet, a phytopharmaceutical formulation, is recommended for comprehensive management of urolithiasis and urinary tract infections (UTI). Cystone tablet expels kidney stones and ureteric stones, and prevents their recurrence. Cystone tablet is safe and effective in the management of pediatric urolithiasis and UTI, and causes significant reduction of associated symptoms.

Composition

Each Cystone tablet contains:

Exts.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shilapushpa (Didymocarpus pedicellata)</td>
<td>130 mg</td>
</tr>
<tr>
<td>Pashanabheda (Saxifraga ligulata)</td>
<td>98 mg</td>
</tr>
<tr>
<td>Manjishtha (Rubia cordifolia)</td>
<td>32 mg</td>
</tr>
<tr>
<td>Nagaramusta (Cyperus scariosus)</td>
<td>32 mg</td>
</tr>
<tr>
<td>Apamarga (Achyranthes aspera)</td>
<td>32 mg</td>
</tr>
<tr>
<td>Gojiha (Onosma bracteatum)</td>
<td>32 mg</td>
</tr>
<tr>
<td>Sahadevi (Vernonia cinerea)</td>
<td>32 mg</td>
</tr>
</tbody>
</table>

Pdrs.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hajrul yahood Bhasma</td>
<td>32 mg</td>
</tr>
<tr>
<td>Shilajeet (Purified)</td>
<td>26 mg</td>
</tr>
</tbody>
</table>

Processed in Vanatulasi (Ocimum basilicum), Gokshura (Tribulus terrestris), Lajjalu (Mimosa pudica), Kulartha (Dolichos biflorus), Balam (Pavonia odorata), Joratoota (Equisetum arvense), and Shaka (Tectona grandis) seed.

Clinical Pharmacology

Cystone tablet has antilithiatic and lithotriptic, pH-renormalizing, diuretic, antimicrobial, anti-inflammatory, demulcent, spasmolytic, antioxidant, and tonic actions.

The antilithiatic action of Cystone prevents the deposition, accumulation, and supersaturation of calculogenic chemicals in urine. Cystone also controls oxamide absorption from the intestine. Cystone corrects the crystalloid–colloid imbalance. Cystone inhibits calculogenesis by reducing the stone-forming substances like oxalic acid, calcium hydroxyproline, etc. The lithotriptic action of Cystone helps in the dissolution of calculi. Cystone causes disintegration of the calculi and crystals by acting on the mucin, which binds the particles together. Cystone offers diuretic action and flushes small stones from the urinary tract.

The pH-renormalizing action of Cystone provides cooling action in the urinary system and relieves burning micturition. Cystone provides antimicrobial action against common urinary pathogens responsible for recurrent UTI.

The anti-inflammatory action of Cystone helps reduce inflammatory changes in the mucosa of the urinary tract, as seen commonly in UTI. The demulcent action of Cystone soothes and protects the irritated or inflamed internal tissues of the urinary tract. The antioxidant action of Cystone prevents free radical damage to the urinary tract. The antispasmodic and anti-inflammatory actions of Cystone provide relief from associated symptoms of urolithiasis and UTI.

Indications

- For the prophylaxis and treatment of adult and pediatric urolithiasis:
  - Calcium oxalate stones
  - Calcium phosphate stones
  - Uric acid and urate stones
- Crystalluria
- Prevention of postlithotripsy recurrence
- As an adjuvant in:
  - Acute and chronic UTI
  - Recurrent UTI
  - UTI during pregnancy
  - Nonspecific urethritis
  - Cystitis
  - Burning micturition
  - Hyperuricemia
  - Nonspecific dysuria

Dosage

Urolithiasis and crystalluria (adult and pediatric): Two tablets twice
daily till the stone passes out, or till symptoms subside.

**Preventing recurrence after surgical removal or passage of stone:** One tablet twice daily for 6 months.

**Urinary tract infections including recurrent UTI:** One tablet twice daily until the infection is cleared.

**Burning micturition:** One tablet twice daily till the symptoms subside.

Dosage may be titrated depending on the severity and chronicity of the disease.

**Adverse Effects**
No adverse effects have been reported.

**Contraindications**
No absolute contraindications.

**Special Precautions**
It is advisable not to recommend Cystone tablet in complete ureter obstruction.

**Drug Interactions**
No clinically or biochemically significant drug interactions have been reported.

**Presentation**
Sealed pack of 60 tablets.

**Pharmacological Actions of Principal Ingredients**

1. **Antilithiatic and lithotriptic actions:**
Cystone tablet exhibits antilithiatic action that helps to prevent the deposition, accumulation, and supersaturation of calculogenic chemicals in urine, and thus inhibits calculogenesis. It corrects the crystalloid–colloid imbalance.

Cystone tablet possesses lithotriptic action that dissolves the mucin, which binds stone particles.

*D pedicellata, D biflorus, S ligulata, T terrestris,* and *E arvense* prevent the deposition, accumulation, and supersaturation of calculogenic chemicals in urine, while Hajrul yahood bhasma has lithotriptic property.

*R cordifolia* has ruberythric acid, which dissolves oxalate stones present in the urinary tract, thereby facilitating their expulsion without recourse to surgery.

2. **pH-renormalizing action:**
Cystone tablet renormalizes the urinary pH and relieves burning micturition.

*E arvense* renormalizes and maintains the urinary pH within the alkaline range—from 7.5 to 8.0.

3. **Diuretic action:**
Cystone tablet offers diuretic action and flushes small stones and gravels.

*D pedicellata, S ligulata, A aspera, O bracteatum, T grandis,* and Hajrul yahood bhasma have potent diuretic actions.

*C scariosus* exhibits diuretic activity, and is also useful in maintaining genitourinary health.

4. **Antimicrobial action:**
Cystone tablet has broad antimicrobial action against common urinary pathogens.

*S ligulata, R cordifolia, O basilicum, T terrestris,* and *E arvense* have broad-spectrum antimicrobial actions against common urinary pathogens responsible for recurrent UTI.

5. **Anti-inflammatory action:**
*C scariosus, R cordifolia, V cinerea, Shilajeet (Purified), O basilicum, E arvense,* and *S ligulata* have anti-inflammatory activities.

6. **Demulcent action:**
*S ligulata and P odorata* have demulcent property due to high content of mucilage, and hence, soothe and protect the irritated or inflamed internal tissues.

*O bracteatum* is a demulcent, and is useful in bladder irritation and retention of urine.

7. **Spasmolytic action:**
Cystone tablet exhibits spasmylytic activity and relieves renal colic.

*O bracteatum* is a powerful antispasmodic agent.

8. **Antioxidant action:**
*R cordifolia, O basilicum, E arvense,* and *T grandis* are strong antioxidant agents.

9. **Tonic action:**
Cystone tablet has tonic property that improves and tones the urinary tract.

Shilajeet (Purified) treats urinary disorders due to its tonic activity.

*C scariosus* is useful in maintaining genitourinary health due to its tonic activity.
Renalka®
(SYRUP)
The coolant of the urinary tract

Introduction
Renalka, a phytopharmaceutical formulation, is a safe and effective alkalizer which not only relieves burning micturition, but also soothes inflamed urinary mucosa. Renalka restores normal urinary pH and normalizes the frequency of micturition. Renalka is effective for long-term prophylaxis of urinary tract infection (UTI).

Composition
Each 5 mL of Renalka syrup contains:
- Gokshura (Tribulus terrestris) 50 mg
- Varuna (Crataeva magna) 50 mg
- Sariva (Hemidesmus indicus) 50 mg
- Musta (Cyperus rotundus) 50 mg
- Ushira (Vetiveria zizanioides) 50 mg
- Shatavari (Asparagus racemosus) 50 mg
- Trikatu 16.5 mg
- Ela (Elettaria cardamomum) 16.5 mg
- Pdr Kshara parpati 75 mg

Clinical Pharmacology
Renalka normalizes the urinary pH. Renalka exhibits beneficial effect by its anti-inflammatory and analgesic, antimicrobial, diuretic, renoprotective, and antioxidant actions.

Thus, Renalka relieves burning micturition, recurrent UTI, and dysuria.

Indications
- Burning micturition
- Cystitis
- Dysuria
- Hematuria associated with UTI
- Recurrent UTI
- As an adjuvant to antibiotics in UTI

Dosage
Children: 1 teaspoonful two to three times daily.
Adults: 2 teaspoonfuls two to three times daily.
Treatment should be continued till the symptoms are relieved.

Adverse Effects
No adverse effects have been reported.

Contraindications
No absolute contraindications.

Drug Interactions
No clinically significant drug interactions have been reported.

Presentation
Pilfer-proof bottles of 100 mL and 200 mL.

Pharmacological Actions of Principal Ingredients
1. Normalization of urinary pH:
   H indicus and Kshara parpati normalize urinary pH, possibly due to alterative and urinary supportive actions.

2. Anti-inflammatory and analgesic actions:
   T terrestris, C rotundus, E cardamomum, and C magna have remarkable anti-inflammatory and analgesic actions that reduce pain, as noticed during dysuria. Their anti-inflammatory action soothes the inflamed mucosa.

3. Antimicrobial action:
   T terrestris and A racemosus have antimicrobial actions against common pathogens involved in UTI of varied etiology.

4. Diuretic action:
   T terrestris, Kshara parpati, C rotundus, and V zizanioides have potent diuretic action that increases blood flow in the kidneys. This, in turn, increases glomerular filtration rate (GFR), and hence the output of urine. This process increases the amount of water excreted through urination, but it does not increase elimination of electrolytes such as sodium, chloride and bicarbonate, as noticed with other diuretics.
This action certainly helps in the pathological states like pyelonephritis, urethritis and cystitis, and also prevents urolithiasis that results from the stasis of urine in kidneys.

5. Renoprotective action:

_H indicus_ has renoprotective effect, which protects against chemically induced nephrotoxicity. _A racemosus_ elevates urinary concentration of magnesium, which is considered one of the inhibitors of crystallization. _T terrestris_ has renoprotective action due to its enhanced chloride and creatinine clearance from the body.

6. Antioxidant action:

_H indicus_ and _A racemosus_ are potent antioxidants, which protect the genitourinary system from oxidative tissue damage.

7. Other beneficial activities:

Trikatu (_Piper nigrum, Piper longum, and Zingiber officinale_) increases the bioavailability of other drugs either by promoting rapid absorption from the gastrointestinal tract, or by protecting the drug from being metabolized/oxidized in its first passage through the liver after being absorbed, or by a combination of both the mechanisms.
Kidney Stones

What are kidneys?
Kidneys are a pair of fist-sized organs on either side of your back, located above the waistline and protected by the ribs.

What are the functions of kidneys?
Kidneys are considered the master chemists of the body.
- They balance the body’s water content and body chemicals.
- They remove waste products from the blood.
- They produce different hormones and chemicals that help produce red blood cells.
- They help the body use vitamin D, which keeps your bones strong and healthy.
- They keep your BP under control.

How does the urinary system work?
The urinary system consists of a pair of kidneys and ureters, the bladder and the urethra.

Kidneys – remove wastes from the blood; Ureters – carry these waste products as urine from the kidneys to the bladder; Urethra – finally passes out the urine from the body.

What is a kidney stone?
A kidney stone is a hard crystal mass that develops from crystals or small particles that dislodge from the urine and build up inside the kidney.

Kidney stones vary in size and can be as small as a grain of sand, or as large as a table tennis ball. Stones may appear in any part of the urinary system.

What factors contribute to kidney stone formation?
Several factors contribute to kidney stone formation:
- Recurrent urinary tract infections
- Drinking too little fluid
- Blockage of the urinary tract
- Consuming too much calcium, red meat, vitamin C in the diet
- Taking medications like calcium-based antacids
- Metabolic disorders such as hyperthyroidism
- Gout and chronic bowel inflammation

What are the symptoms of kidney stones?
- Sudden severe pain in the lower back or lower abdomen that moves to the groin (when a stone moves in the urinary tract). The pain may last for minutes or hours, followed by periods of relief.
- Pain may be accompanied by nausea and vomiting. If there is urinary tract infection as well, symptoms may include fever, chills, sweats, and painful urination.
- There may be evidence of blood in the urine.
- There may be symptoms of urinary tract infection like burning urination, the urge to urinate frequently, and cloudy or foul-smelling urine.

Some people have no kidney stone symptoms until they pass gravel-like stones in their urine.

Who is affected by kidney stones?
Kidney stones affect more men than women (3:1) between 20 and 40 years. Stones usually occur in summer due to dehydration.

Why worry about kidney stones?
The pain associated with kidney stones is unbearable. Stones can lead to kidney failure, which is life-threatening.
Stones that block the kidneys may cause pain. When the block is not removed, the pain may recede in a few days to mislead the sufferer to think that the crisis has passed, when in fact, the blocked kidney has shut down. If left untreated, this could lead to permanent kidney damage.

How are kidney stones diagnosed?

A complete medical examination, x-rays or sonogram, dye injections and ultrasound tests can be used to diagnose kidney stones.

How are kidney stones treated?

Most small stones pass out by themselves within hours or days. To help this process, drink lots of fluid and follow a special diet recommended by the doctor.

Herbal products have proven to be safe and highly effective in preventing the formation of stones and also in disintegrating small stones.

Small stones that do not pass by themselves are treated with high-energy shock waves that break stones to the size of sand grains, so that it can be passed out easily in the urine. Surgery is usually reserved for larger stones.

How can you help prevent the re-formation of kidney stones?

Kidney stones recur in about 50% of cases. If one has more than one kidney stone, he/she is likely to form another. Therefore, prevention is important. One can take steps after talking with doctor inorder to help prevent this.

- Drink plenty of water every hour during daytime, and whenever you get up at night, at least 3 liters per day.
- Avoid large doses of vitamin C (4 gm or more daily) and excessive use of calcium-based antacids.
- If you already have calcium stones, avoid dairy products, tea, chocolate, coffee, nuts, palak (spinach), etc.
- Consume vegetables (radish and cucumber), fruits (watermelon), and cereals (horse gram and barley) frequently.

Dear Doctor,

We hope you found this article useful for your patients. You can order for FREE reprints of this article by using the tear-out card enclosed in this issue, and use them as patient information leaflets in your clinic.

– Editor
World over, there is a growing awareness and concern for health and a strong shift from curative advised health care to preventive health care. To tune in to the trend early on, The Himalaya Drug Company, in March 2002, launched Pure Herbs, a range of individual herb extracts like Tulasi, Neem, and Brahmi.

The Himalaya Pure Herbs brand is a range of specially selected individual herbs that can be used individually to treat/manage specific ailments and maintain wellness of the body. Himalaya Pure Herbs has the pure and concentrated goodness of herbs in the right measure that are scientifically tested and guaranteed for the highest quality and potency.

Benefits of Herbs

Herbs have been used, both as food and medicine, for centuries to eliminate excesses and minimize deficiencies in body. The value of using herbs lies particularly in their mildness to the body. While herbs may provide nutrition to the body, their primary function is to stimulate or improve body functions. Recent research has helped prove and define the pharmacological activities of individual herbs.

Why Pure Herbs?

The herbs that feature in the Pure Herbs range have remarkable benefits and are proven for their authenticity, quality, and efficacy. Everyone can benefit from the goodness of these herbs, irrespective of sex, body type, or state of health and metabolic functions. Pure Herbs, the pure and concentrated strength of a single herb in the right measure, stimulate and improve body functions.

Each Pure Herb is a potent extract and a treasure of active constituents that work by synergistic activity to produce the desired effect. The range gives physicians the choice of prescribing the herbs individually or in combinations to treat various ailments. The readily consumable form (capsules) ensures patient compliance.

Although primarily indicated for lifestyle disorders, Pure Herbs can be used for general maintenance of health and also in chronic disease management. In other words, it provides both preventive as well as curative benefits.

Salient Features of Pure Herbs

The Pure Herbs range is a unique range of potent herb extracts and is perhaps the biggest range of single herbs in the pharmaceutical market. More than half of the herbs in this range are for preventive use and can address problems of modern lifestyle such as stress, oxidative damage, and low immunity. These herbs are cost-effective and can be safely consumed for longer durations. The herbs are packed in smart, user-friendly, and portable containers. Each pack contains 60 capsules and, keeping consumer economics and convenience in mind, is designed for one full month of supply.

Research

Each Pure Herb is the result of stringent monitoring from the farm to the lab. At the lab, Himalaya’s proprietary techniques are used to extract the optimum value of each herb. This is followed by rigorous tests by research and development team for potency and consistency.

The research process begins with raw herbs chosen from traditional texts and from observations and experiences of indigenous plants. The sources of the herbs are subjected to extreme scrutiny in terms of the cultivation process, which is essential organic, quality of crop, methods of harvest, storage, and transportation, etc. The scientific testing and modern extraction process adopted by The Himalaya Drug Company ensures that the benefit of the herb is consistent and without any batch-to-batch variation.

The Pure Herbs Range

The Pure Herbs range includes amalaki as an antioxidant, arjuna for blood circulation, ashwagandha for anti-stress, bael for intestinal comfort, brahmi for alertness, gokshura for improving vitality, guduchi for immunomodulation, haridra for allergy care, kapikachhu for men’s health, karela to regulate metabolism, lasuna for cholesterol protection, manjishtha for skin health, meshashringi for carbohydrate metabolism, neem for skincare, punarnava for urinary support, shallaki for joint pain, shatavari for women’s health, shigru for joint care, shuddha guggulu for cholesterol regulation, sunthi for anti-nausea, tagara as relaxant, trikatu for gastric support, triphala as prokinetic cleanser, tulasi for cough and cold, vasaka for respiratory care, vrikshamla for weight control, and yasthimadhu for gastric care.
Salient features of Himalaya Pure Herbs

- Pure and concentrated herb in capsules with all its attendant benefits
- Well-defined pharmacological actions
- Identification, determination, and validation of active compounds in Pure Herbs using high-performance thin layer chromatography (HPTLC)
- Identification of total marker profile in Pure Herbs with accuracy and specificity using liquid chromatography-mass spectrometry (LC-MS)
- Scientifically tested to avoid batch to batch variation
- Guaranteed for the highest quality and potency

The Pure Herbs range

- Stimulate organic functions
- Possess therapeutic and nutritive values
- Improve and maintain healthy state of the body and mind
**Herbal Notes**

**Allium sativum**

**Sanskrit name/Indian name:** Lasuna  
**English name:** Garlic

Garlic (*Allium sativum*) and Cardiovascular Diseases

Ginter E, Simko V.  

*Allium sativum* is an important component in complementary and alternative medicine. Large segments of population believe in and utilize herbal products even when these have not been as thoroughly researched as *A. sativum*. Experimental and clinical studies confirm that the ancient experience with beneficial effects of *A. sativum* holds validity even in prevention of cardiovascular disorders and other metabolic ills. Most recent data published after year 2000 convincingly point out that garlic and its various forms reduce cardiovascular risk, including abnormal plasma lipids, oxidized low-density lipoproteins (LDL), abnormal platelet aggregation, and a high blood pressure. Stimulation of nitric oxide generation in endothelial cells seems to be the critical preventive mechanism. *A. sativum* may promote an anti-inflammatory environment by cytokine modulation in blood. Cardioprotective effects of dietary *A. sativum* are mediated in large part via the generation of hydrogen sulfide (H2S). *A. sativum*-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide which relaxes vascular smooth muscle, induces vasodilation of blood vessels, and significantly reduces blood pressure. There are data on potential ability of *A. sativum* to inhibit the rate of progression of coronary calcification. *A. sativum* as a dietary component appears to hold promise to reduce the risk of cardiovascular disease.

---

**Terminalia arjuna**

**Sanskrit name/Indian name:** Arjuna  
**English name:** Arjuna

Terminalia arjuna—A Useful Drug for Cardiovascular Disorders

Dwivedi S.  

Ancient Indian physicians used the powdered tree bark of *Terminalia arjuna* Wight & Arn. for alleviating “hritshool” (angina) and other cardiovascular conditions. The stem bark of *T. arjuna* possesses glycosides, large quantities of flavonoids, tannins, and minerals. Flavonoids have been detected to exert antioxidant, anti-inflammatory, and lipid lowering effects while glycosides are cardiotonic, thus making *T. arjuna* unique amongst currently used medicinal plants.

Experimental studies have revealed the bark of *T. arjuna* exerting significant inotropic and hypotensive effect, increasing coronary artery flow, and protecting myocardium against ischemic damage. It has also been detected to have mild diuretic, antithrombotic, prostaglandin E2 enhancing, and hypolipidemic activity. There is ample clinical evidence of its beneficial effect in coronary artery disease alone and along with statin. Considering its anti-ischemic activity and its potential to correct dyslipidemia, reduce left ventricular mass, and increase left ventricular ejection fraction, it is essential to examine the molecular mechanism of its action and its core constituents. Proposition to administer *T. arjuna* along with statins deserves to be explored in depth for defining its place in the overall management and prevention of coronary artery disease.
**Hemidesmus indicus**

**Sanskrit name/Indian name:** Sariva/Anantamul  
**English name:** Indian Sarsaparilla

Natriuretic and Saluretic Effects of *Hemidesmus indicus* Root Extracts in Rats

Gadge NB, Jalalpure SS.

The present study was aimed to investigate the diuretic effects of aqueous (AqE) and ethanolic (EtE) crude extracts of *Hemidesmus indicus* R. Br. roots (family—Asclepiadaceae) using acute model in rats. A single individual dose of AqE and EtE of *H indicus* root (200 mg/kg and 400 mg/kg, po, each), and frusemide and hydrochlorothiazide (25 mg/kg, po, each) as reference diuretic drugs were administered orally to dehydrated rats. Control group rats were fed with normal saline (25 mL/kg, po). All rats were caged in metabolic cages in pairs and their urine output was monitored at 5- and 24-h intervals.

Both extracts significantly increased the urine output in higher doses. Although, the onset of this diuretic action was gradual (within 5 h), it lasted throughout the studied period (up to 24 h). Further, the intensity of diuresis induced by AqE (400 mg/kg) in 5 h was almost similar to that of frusemide and hydrochlorothiazide.

AqE of *H indicus* root also caused marked increase in urinary Na(+) and K(+) levels. However, the routine urinalysis showed nonsignificant alterations in pH and specific gravity by either dose of crude extracts of *H indicus* roots. These effects demonstrate possible diuretic actions of *H indicus* root extracts and support its folklore use in various urinary ailments. Further study need to be done to characterize active phytoconstituents.

**Achyranthes aspera**

**Sanskrit name/Indian name:** Apamarga  
**English name:** Prickly-Chaff flower

Preventive and Curative Effects of *Achyranthes aspera* Extract in Experimentally-induced Nephrolithiasis

Aggarwal A, et al.

The present study was undertaken to evaluate the efficacy of *Achyranthes aspera* in preventing and reducing the growth of calcium oxalate stones in ethylene glycol-induced nephrolithiatic model. Hyperoxaluria was induced in rats using ethylene glycol (EG, 0.4%) and ammonium chloride (1%) for 15 days and was then replaced with EG (0.4%) only. Upon administration of cystone (750 mg/kg body weight) and aqueous extract of *A aspera* (500 and 1000 mg/kg body weight), levels of renal injury markers (lactate dehydrogenase and alkaline phosphatase) were normalized with a decrease in serum urea and serum creatinine. Concurrent treatment reduced changes in the architecture of renal tissue and also decreased the size of crystals, thereby helping in quick expulsion of the crystals. The present results indicated that *A aspera* had an ability to maintain renal functioning and reduced renal injury.
Himalaya Baby Care

Himalaya’s inception can be traced back to the year 1930 when Mr. M. Manal, founder of The Himalaya Drug Company, decided to present Ayurveda to the world in a contemporary form and unravel the mystery behind the 5000-year-old system of medicine. As a result, products of Himalaya are rooted in Ayurveda and backed by years of research—a true synergy of thousands of years of herbal wisdom and modern scientific research. Eight decades later, we have our presence in 67 countries with a range of over 200 products spanning pharmaceutical, personal care, baby care, and animal health. It covers the entire wellness spectrum, offering head-to-toe herbal health care catering to all kinds of people and their different needs.

Liv.52, a liver protective, and Bonnisan, a health tonic for infants and children, are classic examples of innovative research of Himalaya. These products have become a vital part of the family’s health regimen. Bonnisan, for instance, is widely trusted by doctors, pediatricians and mothers, for its safety and efficacy.

With a legacy of research expertise in herbal medicine, including therapeutic products for child health, the next step for Himalaya was “naturally” a range of herbal baby care products.

A comprehensive portfolio that suits every need of your baby, the Himalaya baby care range includes clinically proven pharmaceutical-grade herbal products based on Ayurvedic formulations. Therapeutic herbs such as khus-khus, Indian madder, licorice, and olive have been used in these products to provide gentle care to your baby. Each product, clinically tested by pediatricians in leading hospitals, has 100% herbal actives specially blended to make it safe, effective, mild, and soothing.

The uniqueness of the range lies in understanding the needs of babies and combining it with Ayurveda’s philosophy of child care. Known as “Kaumarabhritiya” or complete care for the child, the philosophy encompasses nursing, nourishing, and supporting the needs of the child to grow into a happy and healthy adult.
Evaluation of Efficacy and Safety of Liv.52 HB Capsules in Chronic Hepatitis B: Double-blind, Randomized, and Placebo-controlled Clinical Study

Banerjee A, Patki PS.

A B S T R A C T

A double-blind, randomized, and placebo-controlled clinical study was conducted to evaluate the clinical efficacy and safety of Liv.52 HB capsules in the treatment of chronic hepatitis B. A total of 28 male and female patients aged between 18 and 65 years with positive HBsAg for at least 6 months and those willing to give informed consent were included in the study. At the initial randomization visit, a detailed medical history and symptomatic evaluation was done. Biochemical investigations included total bilirubin, aspartate and alanine amino transferase, serum alkaline phosphatase, and total proteins. Clinical examinations were repeated every 4 weeks for 24 weeks and biochemical investigations were repeated only after 24 weeks. All the patients were randomized arbitrarily using random table into either Liv.52 HB group (n = 14) or placebo (n = 14). The Liv.52 HB group received 2 capsules twice daily and placebo group received 2 capsules twice daily for 24 weeks. All the patients completed the study and their data were available for analysis. Significant evidence of hepatoprotective effect of Liv.52 HB in patients with HBV infection in terms of clinical response and reduction in biochemical parameters were observed after 24 weeks of treatment. Though, the trial has limitations, the treatment group showed significant clearance of surface antigen as compared to placebo group. The clinical and biochemical recovery in Liv.52 HB group was faster as compared to placebo group, indicating the effect of Liv.52 HB in patients infected with hepatitis B virus. There were no clinically significant adverse reactions either reported or observed during the entire study period. The results of the present study shows clinical benefit of Liv.52 HB and appear promising in the management of Hepatitis B.

Key words: Chronic hepatitis B, Liv.52 HB, placebo

Introduction

Ever since the identification of Australian Antigen in 1967, which is now known as hepatitis B surface antigen (HBsAg), hepatitis B infection has emerged as one of the top 10 leading causes of death in the world. Prevalence of hepatitis B surface antigen (HBsAg) in India varies from 1% to 13%, with an average of 4.7%. Hepatitis B virus (HBV) is present in the blood, saliva, semen, vaginal secretions, menstrual blood, and to a lesser extent, perspiration, breast milk, tears, and urine of infected individuals. A highly resilient virus, HBV is resistant to breakdown, can survive outside the body, and is easily transmitted through contact with infected body fluids. In areas of high endemicity, the most common route of transmission is perinatal or the infection is acquired during the preschool years. In areas of intermediate endemicity, transmission is either perinatal or horizontal.

The route of transmission has important clinical implications, because there is a very high probability of developing chronic hepatitis B (CHB), if the infection is acquired perinatally or in the preschool years. The use of unsafe injections poses a particular public health problem in
developing countries. Contaminated needles cause 8 to 16 million HBV infections each year, compared to 2.3 to 4.7 million hepatitis C virus infections, and 80,000 to 1,60,000 human immunodeficiency virus infections. In areas of low endemicity, most HBV infections are acquired by horizontal transmission in early adult life, that is, through intravenous drug use or unprotected sexual activities.

There are two types of CHB namely HBeAg-positive and HBeAg-negative. Both types are associated with active HBV replication and could produce active liver disease. HBeAg-positive CHB consists of immunoreactive and immunotolerant phases. The immunoreactive phase is mostly seen in adults, with patients having elevated liver enzymes and high levels of viral DNA. The immunotolerant phase is usually seen in children who are infected at birth. They have normal liver enzymes, despite having very high levels of viral replication. The immunotolerant phase may change into the immunoreactive phase. The latent period may be 20 to 30 years for those who are infected at birth and much shorter for those who have been infected in adolescence or adulthood.

Seroconversion from HBeAg-positive to HBeAg-negative and HBeAb-positive states are followed by biochemical, biological, and histological resolution. In most patients, this is a transient phase to the inactive carrier state. The biochemical, virological, and histological abnormalities will persist in 1% to 5% of patients in spite of seroconversion. This group of patients is called HBeAg-negative CHB.

Although chronic HBV infection is highly preventable through vaccination, once it has been established, the sole option for long-term liver disease is treatment. The goals of treatment in CHB infection are sustained viral suppression, normalization of SGPT levels, and improvement in liver histology leading to long-term reduction in the risk of cirrhosis and hepatocellular carcinoma.

Ongoing therapies of hepatitis B (interferon, lamivudine, and most recently introduced adefovir dipivoxil) have limited long-term efficacy. Improvement in treatment options will reduce morbidity and mortality for some individuals who are chronically infected. Ayurveda, an indigenous system of medicine in India, has a long tradition of treating liver disorders with plant drugs. In the present study, Liv.52 HB capsule was evaluated for the efficacy and safety in management of chronic hepatitis B. Liv.52 HB is a herbal formulation consisting of 125 mg each of hydroalcoholic extracts of the herbs Cyperus rotundus and Cyperus scariosus.

Aim

The present study was planned to evaluate the clinical efficacy and safety of Liv.52 HB capsules in the treatment of chronic hepatitis B.

Study design

This study was a double-blind, randomized, and placebo-controlled clinical study conducted at Medical College, Kolkata, India. The study protocol, case report forms, regulatory clearance documents, product-related information, and informed consent form were submitted to the “Institutional Ethics Committee” and were approved by the same.

Material and Methods

Inclusion criteria

A total of 28 male and female patients aged between 18 and 65 years with positive HBsAg for at least 6 months and those willing to give informed consent were included in the study. The serum glutamic pyruvic transaminase (SGPT) levels of these patients should be within 6 times the upper limit of the normal at the screening visit.

Exclusion criteria

Patients with severe decompensated liver disease (defined by serum albumin ≤36 g/dL, bilirubin ≥15 g/dL, prothrombin time ≥2 second prolonged or a history of ascites, variceal hemorrhage or hepatic encephalopathy) and pancytopenias (defined as hemoglobin <11 g/dL, white cell count <4000/mm^3) were excluded from the trial. Patients with coinfection of hepatitis C virus; history of hepatocellular carcinoma, severe hypertension, serious cardiac failure of grade III or more, or renal failure; endocrine disorders like hyperthyroidisms, hypogonadism or Cushing’s syndrome; diabetes; and bone malignancy with pathological fractures and patients on drugs such as corticosteroids, methotrexate, or heparin were excluded from the study. Patients with a history of using interferon or antiviral agents were also excluded. Women of child-bearing age who were not willing to follow the adequate contraceptive method and lactating women were excluded from the trial.

Study procedure

At the initial randomization visit, a detailed medical history and symptomatic evaluation was done. This examination was done especially to score the severity and grading of symptoms such as icterus for evidence of clinical jaundice, anorexia, nausea and vomiting, fatiguability, and weight loss. All the patients were routinely screened and subjected to biochemical investigations.

Biochemical investigations included total bilirubin, aspartate and alanine amino transferase, serum alkaline
phosphatase, and total proteins. Clinical examinations were repeated every 4 weeks for 24 weeks and biochemical investigations were repeated only after 24 weeks. All the patients were randomized arbitrarily using random table into either Liv.52 HB group (n = 14) or placebo (n = 14). The 2 groups were similar with regard to the demographic data, serological parameters, and biochemical investigations. The Liv.52 HB group received 2 capsules twice daily and placebo group received 2 capsules twice daily for 24 weeks.

**End points**

The primary end point was HBsAg clearance. Secondary end points included HBV DNA levels and SGPT normalization to 40 IU/L at the end of treatment.

**Statistical analysis**

Statistical analysis was carried out using GraphPad Prism, Version 4.03 for windows, GraphPad Software, San Diego, California, USA. Biochemical parameters were analyzed using paired t test for within the group comparison and unpaired t test for between the group comparisons. The values are expressed as mean ± SD. Serological parameters were analyzed using Fisher's exact test. The minimum level of significance was fixed at a 95% confidence limit and a 2-sided "P" value of <.05 was considered significant.

**Adverse events**

All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "unrelated" (follows a reasonable temporal sequence from the administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state).

Patients were allowed to voluntarily withdraw from the study, if they so desired without assigning reasons. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Noncompliance (defined as failure to take <80% of the medication) was not regarded as treatment failure, and reasons for noncompliance were noted.

**Results**

A total of 28 patients (18 males and 10 females) with a mean age of 35.90 ± 10.60 years participated in this double-blind, placebo-controlled, clinical study (Table 1). There was no statistical difference in the demographic characters between the Liv.52 HB group and placebo groups.

All the patients completed the study and their data were available for analysis. The significant evidence of hepatoprotective effect of Liv.52 HB was seen in patients with HBV infection, in terms of clinical response, reduction in biochemical and serological parameters.

The clinical effects of Liv.52 HB started to appear as early as 12 weeks and by 24 weeks most of the patients showed a significant improvement in appetite. Clinical reduction of icterus was observed as early as 12 weeks. The effect was also linked with the disappearance of nausea and vomiting from the 12th week onwards. As appetite improved, the easy fatigability of patients was reduced from the 12th week onwards. After starting treatment, patients did not display further evidence of weight loss. It was evident that Liv.52 HB showed a hepatoprotective activity in controlling the early symptoms of HBV infection (Table 2). Though improvements in clinical symptoms were observed in the placebo group, the values were not clinically significant (Table 3).

Investigations on the biochemical parameters demonstrated evidence of a significant improvement in bilirubin, albumin, SGPT, and alkaline phosphatase. From the demographic data, serum ALT levels were almost similar in the 2 groups. The primary end point was HBsAg clearance, and at the end of 24 weeks the HBsAg was negative in 4 (28.57%) of 14 patients in the Liv.52 HB group and in 1 (7.14%) of 14 patients in the placebo group. The difference was statistically significant (Table 4).

**Table 1. Demographic Details**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.90 ± 10.60</td>
</tr>
<tr>
<td>Male:Female</td>
<td>18:10</td>
</tr>
<tr>
<td>History of smoking</td>
<td>16</td>
</tr>
<tr>
<td>History of alcohol consumption</td>
<td>19</td>
</tr>
<tr>
<td>Diet (vegetarian/nonvegetarian)</td>
<td>16/12</td>
</tr>
</tbody>
</table>

**Table 2. Results of Clinical Observations with Liv.52 HB Treatment (Mean ± SD)**

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>At entry</th>
<th>Posttreatment</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
<th>20 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>0.58 ± 0.14</td>
<td>0.88 ± 0.09</td>
<td>1.08 ± 0.11</td>
<td>1.69 ± 0.22</td>
<td>1.98 ± 0.20</td>
<td>2.18 ± 0.12</td>
<td>2.48 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.62 ± 0.12</td>
<td>0.51 ± 0.08</td>
<td>0.36 ± 0.09</td>
<td>0.24 ± 0.04</td>
<td>0.12 ± 0.03</td>
<td>0.06 ± 0.00</td>
<td>0.02 ± 0.00</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.75 ± 0.07</td>
<td>0.58 ± 0.14</td>
<td>0.49 ± 0.11</td>
<td>0.38 ± 0.16</td>
<td>0.31 ± 0.06</td>
<td>0.23 ± 0.09</td>
<td>0.16 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>0.78 ± 0.11</td>
<td>0.54 ± 0.06</td>
<td>0.46 ± 0.09</td>
<td>0.39 ± 0.04</td>
<td>0.30 ± 0.09</td>
<td>0.24 ± 0.08</td>
<td>0.22 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>1.92 ± 0.07</td>
<td>1.18 ± 0.09</td>
<td>0.95 ± 0.08</td>
<td>0.75 ± 0.12</td>
<td>0.45 ± 0.04</td>
<td>0.12 ± 0.03</td>
<td>0.08 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

*P<.001 as compared to “at entry” values. *P<.05 as compared to “at entry” values.
phosphatase (ALP) levels in Liv.52 HB-treated patients. The mean total bilirubin of 4.361 ± 3.704 mg/dL at entry was improved to 0.910 ± 0.406 mg/dL at the end of the treatment with significance of P<.005 and P<.019, respectively. Though there was reduction in SGOT and total protein levels, the values were not statistically significant in Liv.52 HB-treated patients. However, in placebo group, there was no improvement in bilirubin levels. There was reduction in the levels of albumin and total protein, but the values were not statistically significant (Table 4).

Before the treatment, HBsAg was detected in all the patients. In 9 of the 14 patients, HBsAg became undetectable in Liv.52 HB after 24 weeks of treatment and this difference was statistically significant (P<.02). Only 2 patients showed HBSAg-negative at the end of 24 weeks of treatment in placebo group. At entry, 10 of the 14 patients were detected positive for HBV DNA and after 24 weeks of treatment with Liv.52 HB, all the 10 cases were negative for the same (P<.05). Only 4 patients showed negative for HBV DNA out of 10 patients in the placebo group at the end of treatment (Table 5).

Clinical characteristics, biochemical investigations, and serological parameters showed that the group receiving Liv.52 HB had significantly better results than those receiving placebo. There were no clinically significant adverse reactions either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported.

<table>
<thead>
<tr>
<th>Table 3. Results of Clinical Observations with Placebo Treatment (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical symptoms</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Appetite</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Effect of Liv.52 HB on Biochemical Parameters (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1 Bilirubin (mg/dL)</td>
</tr>
<tr>
<td>2 Albumin (gm/dL)</td>
</tr>
<tr>
<td>3 Total protein (gm/dL)</td>
</tr>
<tr>
<td>4 Fall in SGOT levels (U/L)</td>
</tr>
<tr>
<td>5 Fall in SGPT levels (U/L)</td>
</tr>
<tr>
<td>6 Fall in ALP levels (U/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Serological Parameters at the End of the Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1 HbsAg</td>
</tr>
<tr>
<td>2 HbeAg</td>
</tr>
<tr>
<td>3 HBV DNA</td>
</tr>
</tbody>
</table>

Discussion

Despite the existence of safe and efficient vaccines against Hepatitis B infection for almost 20 years, HBV infection remains a major public health problem worldwide, with 400 million chronic carriers, who are exposed to the risk of developing liver cirrhosis and hepatocellular carcinoma.14,15 Currently available treatment for CHB are associated with their own limitations. Conventional therapies like α-interferon and lamivudine, which are expensive at present, are associated with dose limiting side effects in the management of CHB.16–18 The issues to be considered include efficacy, safety, resistance, and cost.19

The beneficial results observed in this study in Liv.52 HB group compared to placebo could be due to synergistic actions of the herbs, Crotalus and C. scariosus present in the study drug. The roots and rhizomes of Crotalus is useful in the treatment of different
diseases like chronic diarrhoea, inflammation, skin rashes, and excess bleeding. It also has antiestrogenic, antimicrobial, anthelmintic, antihistaminic, antiemetic, antipyretic, and antidiabetic activities. The roots of *C. scariosus* have a folkloric reputation as a cordial, tonic desiccant, emmenagogue, diaphoretic, and diuretic. It remained to be an important ingredient of several prescriptions used in indigenous system of medicine to treat a variety of diseases including diarrhoea, epilepsy, fever, gonorrhoea, syphilis, and liver damage. The results of the present study showing clinical benefit of Liv.52 HB appear promising in the management of hepatitis B.

**Conclusion**

The present study showed significant evidence of hepatoprotective effect of Liv.52 HB in patients with hepatitis B infection in terms of clinical response and reduction in biochemical parameters. Though the trial has limitations, the treatment group showed significant clearance of surface antigen as compared to placebo group. The clinical and biochemical recovery in Liv.52 HB group was faster as compared to placebo group indicating the activity of the Liv.52 HB in patients infected with hepatitis B virus. There were no clinically significant adverse reactions either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. The results of the present study showing clinical benefit of Liv.52 HB appear promising in the management of hepatitis B.

**References**

The product Liv.52 is very good, and I am prescribing it regularly for over 5 decades now. Many chronic cases of hepatic congestion and constipation showed very good results with Liv.52. Also, Liv.52 is safe during pregnancy. Therefore, I prescribe Liv.52 in hyperemesis during pregnancy. The services offered by The Himalaya Drug Company are very satisfactory. I also prescribe products like Speman, Evecare syrup, Liv.52 drops, and Liv.52 DS syrup very frequently.

Dr Laxmi Sehgal, Kanpur, Uttar Pradesh

I have worked on jaundice in pregnancy, and use of Liv.52 in cholestatic jaundice. I was a teacher in the Institute of Post Graduate Medical Education and Research (PG teaching) for over 20 years, where I had a very good experience with Liv.52 in many cases of jaundice and pregnancy. Liver biopsy tests show that Liv.52 reduces fatty changes in liver cells.

Dr Arun Kumar Mitra, Kolkata, West Bengal

Liv.52 is highly beneficial in hepatobiliary disorders. Liv.52 drops and syrup are liked by children, especially those who refuse diet. For past 50 years, Liv.52 tablets, syrup, and drops have helped me treat dyspepsia and jaundice in patients of all age groups.

Dr Habib Ullah Zargar, Srinagar, Kashmir

Liv.52 acts as a good appetizer and cholagogue, and has excellent antiviral property. The drug is cost-effective, easy to administer, and has very good patient compliance. A challenging case of infective hepatitis was successfully treated with Liv.52. It works remarkably without any side effects.

The services and products offered by The Himalaya Drug Company are very good.

Dr Chakravorty KK, Kolkata, West Bengal

Liv.52 is the most widely used medicine in viral hepatitis and other chronic liver disorders. It was prescribed even in Iran, where I stayed during the 1990s. Liv.52 is a wonder drug both in terms of its action and brand reputation.

In a challenging case of hepatic precoma, Liv.52 significantly shortened the prothrombin time and the patient recovered completely.

Products of The Himalaya Drug Company are very effective.

Dr Mukhtar Hussain Hakim

Aligarh, Uttar Pradesh

I have been prescribing Liv.52 for almost 50 years to patients with infective hepatitis, alcoholic cirrhosis of liver, and chronic liver disease, and children to improve appetite and establish well-being. I have treated a large number of patients with alcoholic liver cirrhosis successfully with Liv.52. The Himalaya Drug Company provides satisfactory service and offers indigenous drugs.

Dr Malvi H, Bhopal, Madhya Pradesh

Liv.52 works best for hepatomegaly, anorexia, cirrhosis of liver, flatulence, and hyperacidity (esophageal reflux). I have successfully treated a case of hydatid cyst (liver) with Liv.52. The patient was 75% cured within 4 months of treatment.

The services rendered by The Himalaya Drug Company are the best.

Dr Gajender Kumar Verma

Bikaner, Rajasthan

I have known Liv.52 for the past 15 years. I am extensively recommending Liv.52 tablets
for patients with alcoholic liver disease and hepatitis, and getting encouraging results. Liv.52 helps reduce hospital stay and recovery period.

The products of The Himalaya Drug Company are trustworthy and reliable due to the amount of research work that goes behind them. The services rendered by the company are excellent.

Dr Premandidhi Panda, Bhubaneshwar, Orissa

Liv.52 arrests fatty infiltration in chronic alcoholic patients. Also, it is a very effective drug for patients with drug toxicity. Healthy weight gain has been noted in more than 75% cases using Liv.52 DS.

I have treated more than 30 cases of jaundice with liver cirrhosis with Liv.52 DS. It has been very effective in treating drug-induced hepatitis in tubercular patients on antitubercular drugs. Clinical trials on cases with liver cirrhosis and drug-induced hepatitis have shown marked improvement in successive liver biopsies in 35 patients. Liv.52 is a very potent hepatoprotective medicine. I have been recommending it since 1969.

Dr Sarkar SK, Jaipur, Rajasthan

I have been practicing as a physician for the last 10 years. During this span of time, I have prescribed Liv.52 to a variety of patients with viral hepatitis, drug-induced hepatitis, jaundice and anorexia during pregnancy, cirrhotic conditions, and also as an adjuvant to chemotherapy. I have found Liv.52 to be very effective in these conditions.

About 3 years ago, I came across a female tubercular patient who had been treated with antitubercular drugs. Liver function tests revealed high levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and serum bilirubin. I put her on Liv.52 syrup (2 teaspoonsful BID for 1 month), after which her ALT, AST, and serum bilirubin levels reduced significantly to normal.

It has been a pleasure to extend my support to The Himalaya Drug Company. The services provided to me by the company are far beyond satisfactory.

Dr Santosh Kumar, Agra, Uttar Pradesh

Liv.52 is the no. 1 drug prescribed for viral hepatitis by every doctor. I am prescribing Liv.52 since the beginning of my clinical practice. As a supportive medicine, Liv.52 is helpful in viral hepatitis, alcohol-induced hepatitis, and drug-induced hepatitis.

All the drugs from The Himalaya Drug Company are well-known among all doctors. I have been prescribing nearly every product of the company since its introduction and getting good responses.

Dr Rajesh G Agrawal, Surat, Gujarat

Liv.52 is a time-tested natural product, formulated with ancient wisdom and modern technology. It is ideal for hepatobiliary disorders and is going strong. Liv.52 is a product, which physicians prescribe with confidence. I am successfully meeting the challenge of treating liver diseases with Liv.52 everyday for over 3 decades.

The Himalaya Drug Company provides quality products and efficacious formulations that are within the reach of cross-sections of society across the globe. The service rendered is excellent.

Dr Kamath KSV, Bangalore, Karnataka

I am using Liv.52 for the past 40 years and have found it to be very effective, especially during pregnancy. Liv.52 prevents constipation, improves appetite, and promotes digestion. Chronic constipation is common during pregnancy. All my patients felt better after taking Liv.52.

Dr Pratima Patnaik, Bhubaneshwar, Orissa

Liv.52 is a reliable, efficacious, and accepted drug of choice in a wide range of liver diseases. Apart from hepatitis, I also prescribe Liv.52 to prevent drug-induced liver damage in patients on antitubercular therapy or any prolonged drug regimen. I have treated few cases of chronic, recurrent, and severe hepatitis successfully with Liv.52 and observed good remission rates.

Excellent services are provided by The Himalaya Drug Company. They bring the nature’s therapeutic bounty to the common man in a scientific manner.

Dr Sanjiv S Gupta, Thane, Maharashtra

I prescribe Liv.52 regularly for different liver ailments. I have used Liv.52 as an hepatoprotective, antiviral, choleretic, antioxidant, immunomodulator, and appetite-stimulant. A 72-year-old former bureaucrat had come to consult me in 2005. He was an excessive alcohol drinker. When I enquired about his liver status, he said he had been drinking alcohol for the last 40 years, and also took 2 tablets of Liv.52 every day. I recommended liver function tests and ultrasound scanning to check his liver condition. It was noted that ALT, AST, and albumin levels were normal, and there was no cirrhosis. His appetite was also fine. Liv.52 protected his liver for all these years. Thanks to Liv.52.

I find the products and services of The Himalaya Drug Company to be very good.

Dr Brahmamand Nayak, Bangalore, Karnataka
Book

Urolithiasis: Medical and Surgical Management of Stone Disease
Nakada S, Pearle M

Publisher: Taylor and Francis, 2009
ISBN: 1841846880, 9781841846880
Price: $163.50
Length: 290 pages

A thorough knowledge of the pathogenesis and pathophysiology of urolithiasis is critical in order to understand and implement treatment strategies to prevent stone formation. Likewise, a working knowledge of the surgical treatments, instrumentation, and outcomes is necessary to arm patients with sufficient information to make an informed decision and to provide the appropriate treatment modality for a given stone situation.

In Urolithiasis: Medical and Surgical Management, the authors provide a complete guide to the management of stone disease from both a medical and surgical prospective. This book should be an invaluable resource for those who treat stone disease in any capacity, whether surgically or medically, acutely, or long term.

Oxford American Handbook of Urology
Albala DM, et al.

Publisher: Oxford University Press, 2011
ISBN: 9780195371390
Price: $47.07
Length: 720 pages

The Oxford American Handbook of Urology provides authoritative, point-of-care guidance on all aspects of the field, covering both benign and malignant conditions, as well as medical and surgical management. Incorporating diagnosis and treatment advice from established, published guidelines as well as drawing from the experience of 4 seasoned urologists, the book’s concise and accessible format quickly guides the reader to desired information on common signs and symptoms, incontinence, cancer, infections, and infertility plus key information on trauma, urologic emergencies, and pediatric urology. It is an invaluable resource for medical students and residents as well as a useful reference for practitioners.
**The Urology Foundation**

http://www.theurologyfoundation.org/

The Urology Foundation supports medical education and scientific research to improve the diagnosis, treatment, and management of patients with urological diseases such as cancer and infection of the prostate gland, kidney, bladder and testes, male infertility, erectile dysfunction, and incontinence.

Established in the 1995 as the British Urological Foundation (BUF), the foundation encourages international collaboration in the development and implementation of medical education programs and sharing of best practice. Research into causes of urological disease and development of new treatments are urgently needed. The foundation funds a range of medical education programs and full-time research posts to enable urologists to have access to cutting edge clinical practice, surgical techniques, and research in the UK and centers of excellence throughout the world, thus improving the management of patients with urological disease.

**The European Association of Urology**

http://www.uroweb.org/

The European Association of Urology (EAU) represents the leading authority within Europe on urological practice, research, and education. Over 16,000 medical professionals have joined its ranks and help to create forward-looking solutions for continuous improvement, professional growth, and knowledge sharing. The mission of EAU is to raise the level of urological care throughout Europe and beyond.

The EAU delivers training, stimulates research, and broadcasts information. The EAU’s scientific publications encourage discussion and its expert recommendations guide urologists in their every-day practice.
Crossword 9

Theme: Products of The Himalaya Drug Company

Across
2. This drug is an effective phytopharmaceutical solution for eye care, recommended for managing various infective and inflammatory ophthalmic disorders. (10)
6. This polyherbal dental formulation (gel) helps in the management of painful mouth ulcers. (5,2)
7. A polyherbal formulation indicated for the management of infantile colic. (9)
8. A pure herb formulation effective in the treatment of pigmentation disorders. (12)
9. This product helps in the management of ejaculation disorders such as premature ejaculation, spermatorrhea, and nocturnal emission. (7)
10. A phytopharmaceutical formulation, with anti-inflammatory and immunomodulatory properties, which potentiates the nonspecific immune responses of the body. (8)

Down
1. A herbal teeth-whitening agent with antiplaque, antibacterial, and astringent properties. (5,5)
3. This drug is useful in the treatment of acute sporadic constipation and constipation associated with hemorrhoids and in pre- and postoperative conditions. (8)
4. A pure herb formulation with anti-inflammatory and antiarthritic properties, indicated for the treatment of arthritis and joint pain. (8)
5. This product helps in preventing the unpleasant after-effects of alcohol. (5,5)

Answers to Medical Crossword 7 (Vol. LI No. 1 Oct-Dec 2011)

Across: 5) Evecare 6) Tentex forte 8) Reosto 9) Liv 52 HB 10) Cystone
Down: 1) Pilex 2) Diabecon 3) Gasex 4) Brosol 7) Rumalaya
Edward Loughborough Keyes: An Early Twentieth Century Leader in Urology

Stahl PJ, et al.

Edward Loughborough Keyes was a renowned urologist, decorated war hero, prolific writer, and beloved professor. Having served as president of the American Association of Genitourinary Surgeons, the American Urological Association, the International Urological Society, and the Clinical Urological Association, Keyes in large part steered the course of urology during the early 20th century.

The researchers of this study reviewed letters, original publications, and historical records pertaining to Dr Keyes found in the New York Hospital archives, the American Urological Association historical record, the medical literature, and the popular press.

Edward Loughborough Keyes, Jr received his MD from Columbia in 1895, and went on to hold academic positions in urology at Georgetown, the New York Polyclinic Medical School, St. Vincent’s Hospital, Memorial Hospital, New York University, and at the Cornell University Medical College, where he spent most of his career. He authored the premier urology textbook of his day, Urology, and published works on a myriad of urological conditions. Dr Keyes served in World War I as consultant in urology to General John J Pershing, commander of the American Expeditionary Force. During the war he and Hugh Hampton Young led modern history’s first public campaign against sexually transmitted disease, and in America he was one of the leaders of the American social hygiene movement from which contemporary sexual education evolved. He spoke Spanish and French fluently, wrote poetry and prose prolifically, and was acclaimed for his good humor. He died at the age of 75 in New York. Edward Loughborough Keyes is remembered as one of the great urologists of the early 20th century.

Adrian Walton Zorgniotti: Renaissance Urologist

Lizza EF.

Adrian Zorgniotti was born on March 3, 1925 and died on July 6, 1994. During his 47 years as a physician, he brought innovation and imagination to the field of urology, especially in the field of erectile dysfunction (ED). Biographical information was obtained from Dr Zorgniotti’s curriculum vitae, his published articles, and his eulogies. Several of his colleagues and peers were also interviewed by telephone. In addition, personal experiences of this author, from the 9 years we spent as associates, and of several other friends were recounted. Dr Zorgniotti’s involvement with the history of urology began in 1970 when he published his first historical treatise on Rome’s first doctor, Arcagathus. He continued his involvement when he served as moderator for the History Forum of the American Urological Association (AUA) from 1975 to 1988 and as Historian for the AUA from 1979 to 1988. This innovator brought vision to the field of ED when he introduced the combination of papaverine and phentolamine as an intracavernous injection for the treatment of ED. He also organized the first International Conference on Corpus Cavernolum Revascularization in 1978 at New York University and published long-term results with this therapy. Adrian Zorgniotti will probably be best remembered by the multitude of urologists whose lives he has touched for his generosity of spirit and for his ability to help shape our careers with a kind gesture, suggestion, or phone call.
In the move to managed health care, the interaction between the occupational health physician and employee/patient has mimicked somewhat the brevity of the medical visit experienced external to the worksite. Whereas, in former days, there was no sharply predetermined time to be devoted to the individual seeking care, today’s hurried schedules usually allow 15 minutes or less per visit.

Such sharp temporal demarcation allows the ailing person to declare his or her health concerns, a hasty examination by the care provider, the issue of appropriate prescriptions for medication and some counsel concerning the clinical findings, with, possibly, allusion to the patient’s inappropriate health-affecting life style. In industry, there may be additional precautions offered concerning the performance of certain job functions in light of the presenting disorder.

While such a visit will meet the physical needs of the patient, rarely are basic emotional, behavioral, family, or interpersonal difficulties explored. Yet, it is the underlying problem that is most bothersome to the client and which has had no inquiry. The employee leaves, still burdened by the unresolved dilemma that he or she may not even connect to the presenting ailment.

An invaluable opportunity to be of true assistance to the patient is passed, often not just because of time or schedule constraints, but because of discomfiture felt by the practitioner in the exploration and guidance required by these problems whose etiology may be completely outside the workplace.

It has been the practice of the writer, on completion of the worker’s visit, to utilize some extra moments to inquire “How are things at home?” or “How are things going on the job?” There is a brief period of silence, followed by a low-pitched “Oh, that son of mine,” or “Things are not so hot at home.” The door is open, thereafter, to exploration of the true problem troubling the individual and to professional guidance for the rectification of the current dysfunction at home or at the workplace.

An employee was shown his x-ray films as part of a survey of personnel exposed to asbestos, past or present. The findings were explained and reassurance was given as to the minimal changes encountered. On completion of the clinical aspects of the visit, the query was placed regarding conditions at home and the response of “Oh, my daughter. . .” was given. Further questioning revealed that the late teenager had not spoken to her family for many months. It was arranged that she visits the occupational health service for an interview.

It was anticipated that the young woman would be an angry, mute, noncommunicative person, with whom interaction would be difficult. To the contrary, on entry, the daughter was bubbling with smiles and energy, talked freely, and welcomed any expressed concerns by her parents. She played guitar, composed music, was highly articulate, and willing to have the family situation rectified. Counseling was initiated and communication reinstalled within the family.

On another occasion, on completion of the clinical aspects of the visit, the same question was put to the employee concerning events other than those at the work setting. An extremely concerned response was given regarding a 15-year-old daughter who had a presumably uncontrollable, spasmodic, persistent, nonproductive cough (48 coughs per minute) and who communicated solely by written notes. She had been studied by 14 specialists at a variety of hospitals without change in the condition. Following the obtainment of records, appropriate referral was made to a university medical center and with indicated clinical tests and
psychotherapy, all difficulties cleared. Subsequently, the young woman became a physician.

In all comparable instances, the employed parent(s) were extremely grateful for the directive care given and for the lifting of the heavy emotional burdens occasioned by difficult situations away from work.

These examples are offered to lend credence to the belief that a few moments of concern about the real problems perplexing workers can be totally rewarding to the occupational health service, the distraught employees’ families and to the involved persons themselves.

In a recent “Piece of my mind” in the Journal of the American Medical Association, the author wrote, “[We] physicians are still incredibly blind to a critical area of professional skill—our ability to listen to and talk with our patient. [The] number one complaint from the patients was always the same—they said that far too often we medical colleagues don’t take the time to really understand how they feel.”

In parallel with this observation is the late Arthur Ashe’s comment in his autobiography, that while serving on hospital boards he had “seen studies of patients’ complaints that list at the absolute top the doctors’ chronic unwillingness to listen to them.”

Practitioners of occupational medicine can readily alter this public view by utilizing those extra moments to seek the true problem behind the patient’s need for help. Many a clinical visit is made without the employee’s ability to, or being given the opportunity to, express the true underlying quandary that is affecting his or her home and family life and job.

May those few extra moments be used to change some seriously damaged lives and restore well-being to troubled employees and their loved ones.
**Research and Development**

**Innovation at Himalaya**

Innovation through research lies at the core of The Himalaya Drug Company (HDC). Over the last 82 years, scientists at HDC have been researching herbs to offer innovative phytopharmaceutical formulations for conditions like hepatitis B, urolithiasis, and debilitating disorders like diabetes and arthritis. Some of our innovative discoveries include:

- **Liv.52**, the company’s flagship brand, is India’s top hepatoprotective and one of the country’s bestselling herbal drugs. In the 1950s, scientists at Research and Development Center of HDC were working on herbal compositions to better liver function. One formulation, coded 52, showed remarkable results in the treatment of hepatitis A. This lead to further testing and soon afterwards Liv.52 was launched in 1955. Currently, Liv.52 ranks among the top 10 pharmaceutical products in India. The drug is also backed by 264 clinical studies and is the only herbal medication with a meta-analysis for infective hepatitis.

- **Cystone**, which is recommended for the treatment of urolithiasis and urinary tract infection, is another major discovery at HDC. The drug has undergone 90 clinical studies and significant results are seen in over 70% of the patients.

- Discovered accidentally, Himplasia was the first herbal formulation indicated for the clinical management of benign prostrate hyperplasia. Himplasia helps in reducing the size of prostrate by approximately 20% in over a period of 3 months, as documented by 11 clinical studies published in peer-review journals.

In the past year, our researchers have discovered potentials of several other herbs for prevention and cure of various other conditions. The team is working on drugs for malaria, women’s disorders, and herpes simplex virus (HSV)/human immunodeficiency virus (HIV-1) co-infections. The research for these conditions is at various pre-clinical stages. Some compositions are being tested on cell lines, others have reached the animal testing stage.

In the last 8 years, the company has filed for 86 global patents and has been granted 7 for innovative discoveries in areas of hair loss, anti-aging, and sun-protection, among others.
Corporate Social Responsibility

Biodiversity

As a herbal healthcare company, The Himalaya Drug Company (HDC) has been making an effort to preserve environmental biodiversity. Our farmers are already trained on sustainable harvesting and local conservation. The last few years, however, have seen HDC engage in biodiversity conservation projects with various organizations across India.

HDC has tied up with the University of Agricultural Sciences (UAS) in Bangalore to promote sustainable herb cultivation, in order to meet our commercial requirements for some widely used herbs, which are facing extinction. We are jointly researching methods to preserve biodiversity and cultivate endangered herb species. This also involves promoting tissue culture of rare and endangered herbs. As part of this collaborative agreement, UAS will provide us with necessary information and research guidance to set up a repository of diversified group of plants with special reference to rare, endemic, endangered, ornamental, medicinal, and economic plants. We are also in the process of setting up a herb garden that will be a center for national and international research activities.

HDC is also working with the Sikkim State Co-operative Supply and Marketing Federation Limited (SIMFED) in India to promote sustainable collection and cultivation of herbs and preserve local biodiversity in the north-eastern state. HDC and SIMFED cultivate herbs through a network of farmers in this region. These farmers are trained in Good Agricultural Practices and other protocols that are strictly adhered to by the HDC. Simultaneously, the herbs are procured by HDC, thereby contributing to the livelihood of local farmers.

A similar project is underway with Aaranyak, an Assam-based organization working on conservation of biodiversity in the north-eastern region of India and Eastern Himalayan range. In the first phase, HDC has identified five herb species that are facing extinction and will be carrying out a scientific survey to assess the situation, along with Aaranyak. In the second phase, the company will cultivate whichever herbs are found viable. The third phase will see HDC procure the herbs for commercial purposes.

In the state of Andhra Pradesh in India, HDC has supplied seeds to the state medicinal board for planting the herb Oroxylum which is under threat due to over exploitation. HDC has also supplied seeds to the state medicinal board for planting this herb in forest areas (original habitat) and maintaining its population.
A couple was celebrating their golden wedding anniversary on the beach in Montego Bay, Jamaica.

Their domestic tranquility had long been the talk of the town. “What a peaceful and loving couple.”

The local newspaper reporter was inquiring as to the secret of their long and happy marriage.

“Well, it dates back to our honeymoon in America,” explained the man.

“We visited the Grand Canyon in Arizona and took a trip down to the bottom of the canyon by horse. We hadn’t gone too far when my wife’s horse stumbled and she almost fell off.

My wife looked down at the horse and quietly said, “that’s once.”

“We proceeded a little further and the horse stumbled again, this time causing her to drop her water. Once more my wife quietly said, “that’s twice.”

We hadn’t gone a half-mile when the horse stumbled for a third time. My wife quietly removed a revolver from her purse and shot the horse dead.

I shouted at her, “What’s wrong with you, woman! Why did you shoot the poor animal like that? Are you crazy?”

She looked at me, and quietly said, “That’s once.”

“And from that moment... we have lived happily ever after.”

With the help of a fertility specialist, a 65-year-old woman has a baby. All her relatives come to visit and meet the newest member of their family.

When they ask to see the baby, the 65-year-old mother says “not yet.”

A little later they ask to see the baby again. Again the mother says “not yet.”

Finally they say, “When can we see the baby?” And the mother says, “When the baby cries.” And they ask, “Why do we have to wait until the baby cries?”

The new mother says, “Because I forgot where I put it.”

“Doctor, doctor! My small son has just swallowed a roll of film.”

“Don’t worry. Let him rest a bit and we’ll wait and see what develops.”

John: How’s your history paper coming?

Peter: Well, my history professor suggested that I use the Internet for research, and it’s been very helpful.

John: Really?

Peter: Yes! I’ve already located 17 people who sell them!
Scientific Publications from The Himalaya Drug Company

To subscribe to any of these publications, please write to us at publications@himalayahealthcare.com
Introducing

The drops of protection...

...that make a difference.

Rx

Septilin®
(DROPS)

Builds the body’s own defense mechanism

The Himalaya Drug Company
Makali, Bangalore 562 123, India

www.himalayahealthcare.com
E-mail: write.to.us@himalayahealthcare.com