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Outcomes and Long-term Follow-up of Patients with Cystine Stones: a Systematic Review

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Abstract

Purpose of Review Cystine stone patients can be difficult to manage with frequent recurrences. We performed a systematic review with a view to assessing interventions, compliance and their long-term outcomes.

Recent Findings Ten retrospective observational studies (253 patients) assessed the outcomes and long-term follow-up of cystine stone patients. The mean length of follow-up was 9.6 years (range 3.5–21.8 years). The overall mean number of surgical procedures/patient was 5.7 (range 2–9.8/patient) with the overall mean number of surgical procedures/patient/year at 0.59 (range 0.22–1.32/patient/year). While open surgery has decreased over the last decade and PCNL has been stable, there seems to be a rise of RIRS during this period.

Summary Patients with cystine stones need periodic interventions for stone recurrences despite medical management, with limited data showing the impact on renal function. While the management is individualised, wide variability exists with often poor and incomplete patient data.

Keywords Urolithiasis · Cystinuria · Cystine stone · Kidney stone disease (KSD) · Outcomes · Recurrence · Ureteroscopy · PCNL

Introduction

Cystine stone patients are amongst the hardest stone patients to manage clinically with a typically young age of disease onset, high recurrence rates and a heavy reliance on compliance with intensive medical therapies [1–4]. The mainstay of management focuses on urinary alkalinisation using medications including potassium citrate, dietary measures including limiting sodium and animal meat intake, and maintaining a generous fluid intake of 4–4.5L/day [5, 6].

Studies published in recent years have made significant headway in characterising the genetic basis of this condition, and work continues on the genotype-phenotype correlation and targets for novel therapies [7, 8, 9•, 10]. However, there have been a relatively small number of studies assessing long-term clinical outcomes of cystinuric patients. It has been promising to see a number of recently published studies making headway in addressing this paucity of outcome data in cystine stone formers, although all studies have struggled to achieve numbers substantial enough to return meaningful

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statistical analysis [11•, 12•]. This is an inherent issue given the relatively rare nature of this disease (making up just 1% of adult urinary tract calculi) [13, 14].

This review analyses long-term follow-up in cystine stone formers with a view to assessing interventions, compliance and long-term outcomes.

Methods

Evidence Acquisition: Criteria for Considering Studies for This Review

Inclusion Criteria

- Studies on cystinuric patients with at least one surgical intervention
- Patients of all ages
- English language articles with long-term follow-up

Exclusion Criteria

- Animal or laboratory studies
- Case reports and review articles
- Studies with non-surgical management

Search Strategy and Study Selection

We performed a systematic review of literature in Cochrane style in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist (Fig. 1) [15]. A literature search was conducted using MEDLINE, EMBASE, Scopus, Cochrane Library, CINAHL and individual urology journals. Search terms including "cystine stone", "cystine calculi", "cystin*", "cystinuric", "cystinuria", "outcomes", "follow-up", "recurrence", "surgical", "ureteroscopy", "PCNL" and "long term" were used individually and in combination using appropriate Boolean operators (AND, OR) in order to maximise yield.

Searches were restricted to English language human-related articles published from January 1980 to December 2018. All observational studies of cystinuric patients with at least one surgically managed confirmed cystine stone episode under long-term follow-up were included, regardless of patient age. Surgical management was classed as percutaneous nephrolithotomy (PCNL), ureteroscopy and lithotripsy (URS), or shockwave lithotripsy (SWL). Authors were contacted wherever full texts were not available. Studies focused solely on medical management and prevention of stones in cystine stone formers, or which lacked follow-up data, or which failed to meet any of the criteria in the data extraction and analysis section, were excluded.

Data Extraction and Analysis

Data extraction was carried out by two authors (SM and BKS) independently, and discrepancy was resolved with mutual consensus. In case of missing data or uncertainty, the authors were contacted directly. Selected studies were assessed for design, aim, inclusion criteria, patient demographics, stone burden, number and type of surgical interventions, stone-free rates (SFR), disease recurrence rates, renal function data, follow-up and any patient-reported outcome measures such as the use of validated quality of life scores. Outcomes of interest included intervention types, SFR and long-term recurrence rates.

Due to a substantial degree of heterogeneity between studies in both design and reporting, analysis was limited to narrative synthesis and pooled analysis of mean results.

Results

A total of ten studies have been reported in the literature which assessed the outcomes and long-term follow-up of cystine stone patients. All studies were of a retrospective observational design. Included studies, along with design and inclusion criteria, are displayed in Table 1.

Demographic Data

A total of 253 patients (range 8–42/study, Table 1) were included. The mean length of follow-up was 9.6 years (range 3.5–21.8 years, Table 1). Five studies reported an average (mean or median) age of diagnosis of cystinuria ranging 15–19.6 years [11•, 12•, 16–18]. Male to female ratio was in favour of females in five studies, males in three studies, 1:1 in one study and not reported in one study. Two studies reported body mass index data for included patients [11•, 12•]. Usawachintachit M et al. reported a mean BMI of 28.6, while Moore S et al. reported 60% of patients in their cohort with a BMI > 25 [11, 12].

Surgical Interventions

Eight studies reported the total number of surgical procedures undertaken (mean 161.8 procedures across studies, range 38–261 procedures), with a mean of 5.7 surgical procedures/patient (range 2–9.8/patient) (Table 2). Seven studies reported the mean number of surgical procedures per patient per year or provided data that made this calculable; the overall mean number of surgical procedures per patient per year was 0.59 (range 0.22–1.32/patient/year). Seven studies gave sufficient

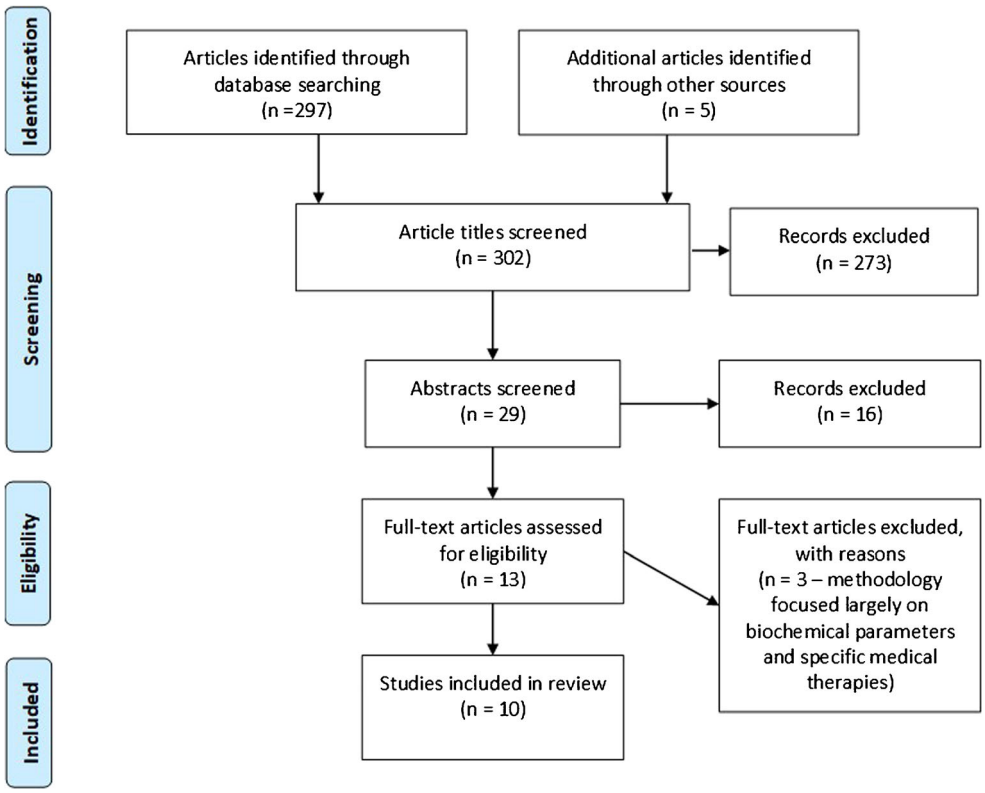

Fig. 1 Systematic review of literature in Cochrane style in accordance with PRISMA checklist

data to assess the precise operative modality used; three studies reported percutaneous nephrolithotomy (PCNL) as the most commonly used operative intervention [12•, 19, 20]; three studies reported retrograde intrarenal surgery (RIRS) as the most commonly used operative intervention [17, 21, 22], while one study reported shockwave lithotripsy (SWL) as the most commonly used [18].

Stone-free rates were reported in eight studies, although exact method of reporting varied considerably. Stone-free rates were reported as 48–86.9%. Of these, only three studies defined what they classified as "stone free" whereas others did not define how they calculated this.

Two studies reported renal function in terms of eGFR, while one reported in terms of creatinine. While one study highlighted significantly reduced eGFR in those who had undergone > 3 surgical interventions ($p = 0.04$) [11], the other showed a non-significantly higher creatinine in those who were non-compliant with medical therapy (who also were shown to have a significantly higher number of surgical interventions per patient, $p < 0.05$) [19].

Patient Compliance and Quality of Life Assessment

Six studies reported patient compliance with medical therapies. Two defined compliance as attendance at > 50% of medical appointments in 1 year, with a 55% compliance rate in one study and 88.6% in the other study [19, 21]. One study assessed reported compliance with taking oral medication, citing 67% compliance in patients taking potassium citrate versus 36% in patients taking penicillamine versus 35% in patients taking bicarbonate [22]. One study assessed reported compliance with dietary advice as well as all types of medication, and of the 10/30 patients for whom the authors reported dietary data, 33.3% were deemed compliant, while, for the 14/30 patients for whom the authors reported medication compliance data, 64% were deemed compliant [16]. One study assessed reported compliance with fluid intake and highlighted that 4/16 (25%) patients were compliant with daily fluid intake > 4 L [11•]. One study did not specify how it recorded compliance [17].

None of the included studies reported long-term quality of life outcomes in these patients. Formal risk of bias assessment was not carried out; however, all studies were limited by their retrospective nature and small sample size.

Discussion

Meaning of the Study

To our knowledge, this is the first systematic review analysing long-term outcomes in cystinuric patients. The data suggests that, during a long-term follow-up, a patient would expect to undergo a mean of 0.59 procedures/year (range 0.22–1.32) for stone recurrences. While open surgery has decreased over the last decade and PCNL has been stable, there seems to be a rise

Table 1 Studies assessing the outcomes and long-term follow-up of cystine stone patients with study design and inclusion criteria

Author	Year of publication	Paper title	Study type	Study inclusion criteria	Number of cystine stone patients included	Mean follow-up period (years)
Usawachintachit M et al.	2018	Clinic outcomes for cystinuria patients with unilateral versus bilateral cystine stone disease	Retrospective case-control	All patients seen at least twice in medical stone clinic with a confirmed history of cystine stones and confirmed cystine stone on analysis	42	8.8
Moore SL et al.	2018	Journey of a cystinuric patient with a long-term follow-up from a medical stone clinic: necessity to be SaFER (stone and fragments entirely removed)	Retrospective observational	All patients seen in the metabolic stone clinic with at least one surgical intervention for cystine stone disease between Jan 1994 and Dec 2014	16	8.6
Yamacake KGR et al.	2016	The challenge of cystine and struvite stone formers: clinical, metabolic and surgical assessment	Retrospective search of prospective database	All patients with a stone episode and complete follow-up between Jan 2006 and June 2011	8	NR
Sfoungaristos S et al.	2015	Cystine stones: a single tertiary centre experience	Retrospective case-control	30 patients who underwent stone treatment for cystine stone between Jan 1972 and Dec 2013 (then matched and paired to oxalate stone formers)	30	NR
Shim M et al.	2014	Multimodal treatments of cystine stones: an observational, retrospective single-center analysis of 14 cases	Retrospective observational	All patients seen with a cystine stone between March 1994 and July 2012	14	6.5
Haritopoulos K et al.	2010	Impact of a metabolic stone clinic on management of patients with cystinuria: 5 years follow-up.	Retrospective observational	All cystine stone patients seen between 1992 and 2008 (pre- and post-introduction of metabolic stone clinic)	35	6.4
Ahmed K et al.	2008	Management of cystinuric patients: an observational, retrospective, single-centre analysis	Retrospective observational	Cystine stone patients treated between 1998 and 2005	30	6
Pareek G et al.	2005	Urological intervention in patients with cystinuria is decreased with medical compliance	Retrospective observational	All patients treated by a single surgeon for cystine stones between 1994 and 2004	20	3.5
Barbey F et al.	2000	Medical treatment of cystinuria: critical reappraisal of long term results	Retrospective observational	All cystine stone patients seen between 1963 and 1998	27	21.8
Chow GK et al.	1998	Contemporary urological interventions for cystinuric patients: immediate and long term impact and implications	Unclear if retrospective or prospective	All patients receiving medical management for cystinuria and at least 1 surgical intervention between Nov 1983 and Feb 1997	31	4.6 (for 21/31 patients) N.B. not included in mean

Table 2 Studies reporting on surgical interventions

Author	Year of publication	Total number of surgical interventions	Total number of surgical interventions per patient	Total number of surgical interventions per patient per year	Intervention type	Number of reported nephrectomies due to stone burden	Number of stone-free patients after treatment course
Usawachintachit M et al.	2018	261	6.2	0.57	112 (42.9%) PCNL 90 (34.5%) RIRS 44 (16.9%) SWL 15 (5.7%) Open	3	NR
Moore SL et al.	2018	49.6	3.1	0.36	9 patients underwent PCNL (4 as solo rx) 6 patients underwent RIRS (2 as solo rx) Majority had combination treatment including SWL	1	9/16 (56%)
Yamacake KGR et al.	2016	NR	3.6	NR	NR	Operative data NR	70%
Sfoungaristos S et al.	2015	NR	(±9.17)	NR	Reported as means, but mostly < 1, unclear as to what figures mean	Operative data NR	NR
Shim M et al.	2014	38 (not including SWL)	2.7 (not including SWL)	0.41	12 (31.6%) PCNL 25 (65.8%) RIRS 1 (2.6%) Open	NR	9/14 (64.3%)
Haritopoulos K et al.	2010	199	3.6	0.56	32 (16.1%) PCNL 67 (33.7%) RIRS 95 (47.7%) SWL 5 (2.5%) Open	NR	48%
Ahmed K et al.	2008	237	7.9	1.32	28 (12%) PCNL 50 (21%) RIRS 143 (61%) SWL 16 (6%) Open	NR	After multiple treatments, 28/30
Pareek G et al.	2005	47	2.35	0.67	21 (44.7%) PCNL 20 (42.6%) RIRS 6 (12.7%) SWL	NR	11/20 (55%)
Barbey F et al	2000	125	4.6	0.22	15 (12%) PCNL 7 (5.6%) RIRS 32 (25.6%) SWL 65 (53.3%) Open	6	13/27 (48%)
Chow GK et al.	1998	61	1.98	NR	41 (67.2%) PCNL 7 (11.5%) RIRS 9 (14.8%) SWL 4 (6.6%) SWL + PCNL	NR	86.90%

of RIRS during this period. Most studies reported a combination of procedures depending on the stone complexity; however, an increasing number of procedures seem to have a detrimental effect on their renal function.

Difficulties in Reporting of Long-term Studies

There is a lack of consensus on the best surgical management of cystine patients. Although surgical intervention has to be targeted, no current guidance exists on these stones. The lack of consensus on the definition of basic measurable outcomes such as SFR, clinically insignificant residual fragments (CIRF) and compliance to treatment makes comparison and standardisation of outcomes even more difficult [23]. Similarly, although cystinuric patients have a high risk of recurrence, there is a lack of consistency on follow-up interval and imaging modality used. Although a handful of studies included renal function information, this is an important parameter which must be a part of monitoring patients especially those who have frequent intervention for recurrences.

Strength and Limitations of Our Study

As cystine stones are rare and management is specialised, our review allows us to understand this disease condition. A generic urolithiasis outcome or follow-up paper may not be entirely representative. This article gives an overview of the recurrences and interventions in cystinuric patients. However, all papers included in our review were retrospective observational studies and thus are prone to bias. Furthermore, there was a large degree of heterogeneity in the design and reporting of all studies, making even narrative synthesis of the results challenging.

Cystine stone disease is a relatively uncommon entity and as such all studies struggle to obtain the quantity of patient data required to obtain meaningful, generalisable results. Our review pools the results of these smaller studies in an attempt to identify common themes in the long-term management of cystinuric patients. A lack of cost analysis and quality of life (QoL) data fails to give the true cost for healthcare providers and patients [24, 25]. Additional information on hospital stay and complications should also be provided [26, 27].

Areas of Future Research

Patients with cystine stones need an individualised management and must be discussed as a part of a stone multidisciplinary team (MDT). Apart from outcome data, patient's QoL must be an integral part of their treatment and follow-up. Being a rare disease, perhaps, the management should be done in selected high-volume endourology centres who are able to offer all types of medical and surgical interventions.

Although, recently, there are more studies and a rise of research interest in cystine stone management, we must invest in prospective multi-centric studies with long-term follow-up to understand the trends of recurrences in patients who have compliant medical treatment and excellent surgical interventions when required. This will also allow the real impact of stone recurrences and intervention on their renal function of this cohort of high-risk patients. A standardised reference on compliance and outcome measures must also be done with some clinical guidance on their long-term follow-up.

Conclusion

Patients with cystine stones need periodic interventions for stone recurrences despite medical management, with limited data showing the impact on renal function. While the management is individualised, wide variability exists with often poor and incomplete patient data which needs to be addressed.

Compliance with Ethical Standards

Conflict of Interest Sacha L Moore, Paul Cook, Vincent de Coninck, Etienne Xavier Keller, Olivier Traxer, Laurian Dragos, and Iqbal S Shergill each declare no potential conflicts of interest. Bhaskar K Somani is a section editor for *Current Urology Reports*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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