TITLE: Computed Tomography Imaging for the Diagnosis of Renal Colic: A Review of Clinical and Cost-Effectiveness

DATE: 14 November 2014

CONTEXT AND POLICY ISSUES

Renal and ureteral stones (urolithiasis) are common problems in primary care practice and affect approximately 10% of the population.[1,2] Renal colic is a typical symptom of urolithiasis and frequently leads to emergency department (ED) visits.[2] Other conditions such as pyelonephritis, pain due to ectopic pregnancy, rupture or torsion of an ovarian cyst, or biliary colic may mimic the severe flank pain caused by urolithiasis.[3] Initial imaging such as helical non-contrast computerized tomography (CT) or ultrasonography (US) can help distinguish urolithiasis from these conditions in patients presenting to the ED with acute flank pain.[3]

An American study showed that the use of CT scans for evaluation of flank pain in the ED signficantly increased (from 19.6% to 45.5%) between 2000 and 2008, while the use of US remained stable (from 5.6% to 6.9%). During that period, the proportion of patients who were diagnosed with a kidney stone remained stable at approximately 20% of those evaluated for flank pain.[4] Previous research indicates that CT is more accurate than US for the diagnosis of urolithiasis; however, it is associated with escalating health care costs and radiation exposure, in particular cumulative doses of radiation in patients who need repeat imaging (e.g. kidney stone formers).[3,5-10] Because of the increased lifetime risk of cancer related to the radiation from CT scans, their use as initial diagnosis of urolithiasis is not recommended for pregnant women and young children.[3,10] Low-dose non-contrast CT imaging allows identification of renal and ureteral calculi with similar sensitivity and specificity as standard CT scans but with signficantly reduced radiation dose.[5] However, low-dose non-contrast CT may not be reliable in detecting small stones, for instance stones less than 2 mm in diameter, or stones in obese patients.[3] US can be performed by a radiologist or at the bedside (point-of-care US) by an emergency physician who has received training in this technique. It is not associated with radiation; however it is less sensitive than CT in detecting stones in kidneys or ureters, especially for stones less than 5 mm in diameter.[8,11-13] Other radiological tests that are less frequently in ED for suspected urolithiasis include plain X-ray, intravenous pyelography, and magnetic resonance imaging. Some of these tests are not appropriate in the initial diagnosis of urolithiasis.[3]

The purpose of this report is to summarize the evidence on the clinical effectiveness and the cost-effectiveness of CT imaging compared with point-of-care US or no formal imaging for the diagnosis of renal colic due to kidney stones.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of computed tomography (CT) imaging for the diagnosis of patients with renal colic due to kidney stones?

2. What is the cost-effectiveness of CT imaging for the diagnosis of patients with renal colic due to kidney stones?

KEY FINDINGS

Limited evidence from one randomized controlled trial suggested that point-of-care ultrasonography and computerized tomography had similar effects on various patient outcomes such as the 30-day incidence of complications or serious adverse events resulting from missed or delayed diagnosis and cumulative radiation exposure, in patients with suspected urolithiasis in the emergency department setting. No economic evaluations were identified to examine the cost-effectiveness of the two technologies in the study population.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 17, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients presenting to the emergency department with potential renal colic due to kidney stones
Intervention	CT imaging
Comparator	Clinically-guided management without formal imaging; Point of care ultrasound
Outcomes	Clinical effectiveness: 30-day incidence of complications or serious adverse events resulting from missed or delayed diagnosis; 6-month cumulative radiation exposure; surgical intervention rates; pain; functional status or quality of life; return to ED; hospitilizations; diagnostic accuracy. Health system costs; cost-effectiveness
Study Designs	Health technology assessment/systematic review/meta-analysis, randomized controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria detailed in Table 1, if they were duplicate publications, if CT imaging was used as a reference standard when evaluating a different imaging technique, if CT imaging was compared with standard US performed by a radiologist, or were published prior to January 2010.

Critical Appraisal of Individual Studies

Randomized controlled trials (RCTs) were assessed using the Downs and Black checklist.[14] Numerical scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 553 citations were identified in the literature search. Following screening of titles and abstracts, 535 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 17 publications were excluded for various reasons, while two publications reporting on one unique study (RCT) met the inclusion criteria and were included in this report. No HTA/systematic review/meta-analysis, non-randomized study or economic evaluation was identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The STONE (The Study of Tomography Of Nephrolithiasis Evaluation) study was conducted in the United States.[15,16] It was a multicenter RCT designed to evaluate the comparative effectiveness of US versus CT for the initial evaluation of flank or abdominal pain in EDs across the country. Adult patients with suspected renal stones and with body weight less than or equal to 285 lbs in men or 250 lbs in women were recuited to the study. Patients with a high risk for

serious alternative diagnoses such as acute cholecystitis, appendicitis, aortic aneurysm or bowel disorders determined by the treating emergency physician were not eligible. Participants were randomized to 1) point-of-care ultrasonography (POCUS) in the ED performed by an emergency physician who had received training recommended by the American College of Emergency Physicians, 2) US in the radiology department or 3) CT in the radiology department. The type of CT imaging was not specified. In total, 2,776 patients were randomized to the three imaging tests, and 2,759 were entered into the analysis, 908 in the POCUS group, 893 in the US group and 958 in the CT group. The patients, health care providers and study investigators were not blinded to the assigned imaging examinations. The patients were followed up for six months after randomization. Three primary outcomes were assessed: the 30-day incidence of high-risk diagnoses with complications that could be related to missed or delayed diagnosis, the 6-month cumulative radiation exposure, and total costs. The results of total costs were not reported in the study and no reason was provided. The high-risk diagnoses with complications were defined as any of the following diagnoses within 30 days after the ED visit: abdominal aortic aneurysm with rupture, pneumonia with sepsis, appendictitis with rupture, diverticulitis with abscess or sepsis, bowel ischemia or perforation, renal infarction, renal stone with abscess, pyelonephritis with urosepsis or bacteremia, ovarian torsion with necrosis, or aortic dissection with ischemia. Cumulative radiation exposure was defined as the sum of the effective doses from all imaging that was performed within six months after randomization. Secondary outcomes included serious adverse events (SAEs), SAEs related to participation in the study, return ED visits and hospitalizations after discharge from the ED, self-reported pain scores in an 11-point visual-analogue scale (higher score indicates more severe pain), and diagnostic accuracy for nephrolithiasis. When assessing diagnostic accuracy, the reference standard was confirmed stone diagnosis, with confirmation either by the patient's observation of the passage of the stone or by the medical chart showing that the stone had been removed surgically. Statistical analyses were performed in the intention-to-treat (ITT) population. A planned sample size of 2,500 patients would have 80% power to detect a 5% between-group difference in events with a prevalence of 10%, 0.34% difference in events with a prevalence of 0.5%, and 0.14 standard deviation (SD) for radiation exposure. Adjustment for multiple comparisons was not reported in the study.

The baseline patient demographic characteristics and disease characteristics were comparable across groups. There was no statistically significant difference in baseline self-reported pain score between groups, suggesting similar severity of the condition in the three groups.

Summary of Critical Appraisal

The RCT found for this report was a multicenter study with sufficient sample size, based on the power calculation presented. The approaches used for randomization are considered appropriate. During the study, patients, health care providers or study investigators were not blinded to the study group assignment. It is unlikely that the unblinding would significantly affect the study outcomes such as the severe complications from missed diagnoses (which were jointly assessed by an independent Data Safety and Monitoring Board and the study investigators), cumulative radiation exposure, return to the ED or hospitalization. It is unclear if it has an impact on the pain score which was a patient-reported outcome. A broad range of outcomes were evaluated including utilization of health care resources and diagnostic accuracy. Data analyses were performed in the ITT population. Losses to follow-up were reported in the study, and the proportion of patients lost to follow-up was low in the three comparison groups (3% to 6%). Sensitivity analysis of study outcomes in patients with complete follow-up data was

conducted, although the results were not reported in the study. Given the small percentage of patients who were lost to follow-up in this study, it is less likely to have a significant impact on the study results. The funding source of this study was reported.

The limitations of the study include not reporting patient's health-related quality of life, and lack of information on the health care costs related to the use of various imaging tests. In addition, the reference standard relied partially on the patient's observation on the passage of the stone; therefore it may not be accurate in case of small stones (some patients might have had a stone they did not remember passing). The reference standard also included confirmation from a medical record of surgically-removed stones. However, surgery is not indicated for all kidney stones. It is possible that the number of patients with renal stones was underestimated, which would bias the results of diagnostic accuracy. The models of CT or POCUS used in the study were not described, therefore it was unclear if different generations of instruments have been used, which may have an impact on the diagnostic accuracy. In addition, the study didn't specify the type of CT scans - whether a conventional-dose CT or low-dose CT was used. There was no information on the frequency of follow-up imaging tests, either US or CT, performed within the 6-month period after randomization. The cumulative radiation in the POCUS group may also depend on the level of training received by the emergency physicians who performed the POCUS examinations, and whether they requested confirmation of the diagnosis by further imaging. Therefore the data of cumulative radiation exposure should be interpreted with caution, as well as the generalizability of the study findings to patients in different health care systems, as well as emergency physicians with various levels of training in conducting POCUS.

Summary of Findings

Details for the study findings are presented in Appendix 2.

In the STONE study, 2,776 patients were randomized to the three imaging tests. Among these, 2,759 were included in the ITT analyses (908 in the POCUS group, 893 in the US group and 958 in the CT group). Seventeen patients withdrew from the study between randomization and data analyses (one in the POCUS group, eight in the US group and eight in the CT group; no reasons were provided for these 17 withdrawals). There were 32 (3.5%), 49 (5.5%) and 32 (3.3%) lost to follow up in the three groups, respectively. A sensitivity analysis of study outcomes in patients with complete follow-up data was conducted, while the results from this sensitivity analysis were not reported.

<u>30-day incidence of complications or serious adverse events resulting from missed or delayed diagnosis</u>

In the STONE study, high-risk diagnoses with complications within 30 days after randomization were reported in 11 patients: six (0.7%) in the POCUS group, three (0.3%) in the US group and two (0.2%) in the CT group. The final diagnosis for these patients included two serious gastrointestinal disorders, eight severe urinary tract infections and one gynecologic emergency. Details of the complications resulting from missed or delayed diagnosis are presented in Appendix 2. There was no statistically significant difference between the three groups, $P = 0.30$. SAEs were reported in 12.4%, 10.8% and 11.2% of patients in the three groups, respectively, $P = 0.50$. Deaths were not reported in the STONE study; therefore we assume that these complications did not result in death.

6-month cumulative radiation exposure

In the STONE study, the cumulative radiation exposure over the course of the 6-month study period was 10.1 mSv in the POCUS group, 9.3 mSv in the US group and 17.2 mSv in the CT group, $P < 0.001$ for the comparisons between POCUS, US and CT.

Surgical intervention rates

Not reported in either publication.

Pain

In the STONE study, self-reported pain was measured at discharge from the ED, at 3-day follow-up and at 7-day follow-up. The pain scores were similar across the groups at the three assessments, ranging from 2.0 to 3.3. There was no statistically significant difference between groups for this outcome.

Functional status/Health-related quality of life

Not reported in either publication.

Return to the emergency department

In the STONE study, the proportion of patients returning to the ED after discharge within six months of randomization was 27.7%, 28.3% and 29.2% in the three groups, respectively. There was no statistically significant difference between groups.

Hospitalization

In the STONE study, there were no statistically significant differences in hospital admission six months after ED discharge: 10.4%, 10.3% and 9.5% in the three groups respectively, $P = 0.80$.

Diagnostic accuracy

In the STONE study, the sensitivity of POCUS, US and CT was 85%, 84% and 86% for detecting renal stones in the three groups, respectively; the specificity was 50%, 53% and 53% for detecting renal stones in the three groups, respectively. No statistically significant differences were found between groups.

Health system costs

Not reported in either publication.

Cost-effectiveness

There were no economic evaluations identified.

Limitations

The literature search did not identify HTAs, systematic reviews or economic evaluations regarding the comparative clinical and cost-effectiveness of CT relative to point-of-care US for evaluating renal colic in an ED setting. Important health outcomes such as the change in health-related quality of life or functional status, or surgical intervention rates were not reported in the included RCT.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence regarding the comparative effectiveness of CT and point-of-care US in evaluating renal colic in the emergency department was limited over the period of literature search. One RCT enrolled 2,776 patients and assessed a variety of patient outcomes and utilization of health care resources in six months. The study findings implied that the two technologies had similar effectiveness in the 30-day incidence of complications or serious adverse events resulting from missed or delayed diagnosis, cumulative radiation exposure, change in pain, return to ED within 6 months, hospitalization after ED discharge, and diagnostic accuracy. Compelling evidence from more trials with stringent reference standards and reporting of associated health care costs is still needed to confirm the comparability between point-of-care ultrasonography and CT scan.

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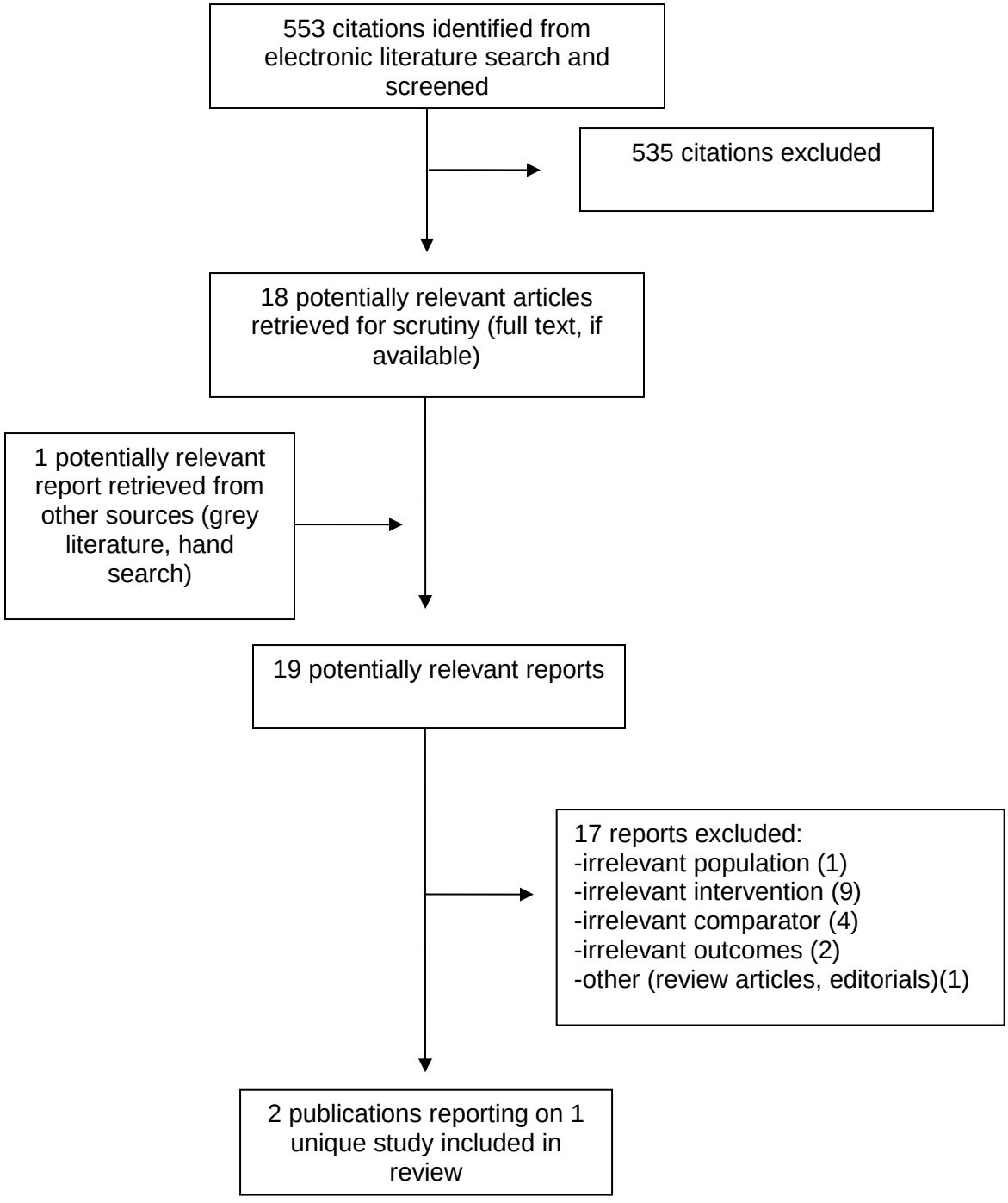
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Findings

First Author, publication year	Main study findings				
Smith-Bindman (STONE), 2014[15,16]	**Outcomes**	**CT N=958**	**POCUS N=908**	**US N=893**	**P value**
	30-day incidence of complications or SAEs resulting from missed/delayed diagnosis, n/N (%)	Complications: 2/958 (0.2) • 1 pyelonephritis/ urosepsis/ bacteremia • 1 urosepsis/ bacteremia SAEs: 107/958 (11.2)	Complications: 6/908 (0.7) • 3 pyelonephritis/ urosepsis/ bacteremia • 1 urosepsis/ bacteremia • 1 small bowel obstruction/ bowel ischemia and resection • 1 diverticulitis with abscess SAEs: 113/908 (12.4)	Complications: 3/893 (0.3) • 1 pyelonephritis/ urosepsis/ bacteremia • 1 ovarian torsion • 1 renal abscess SAEs: 96/893 (10.8)	0.30 0.50
	Radiation exposure, mSv, mean (SD)	17.2 (13.4)	10.1 (14.1)	9.3 (13.4)	< 0.001
	Pain, mean (SD) At discharge At 3-day follow-up At 7-day follow-up	 3.3 (2.9) 3.0 (3.0) 2.0 (2.8)	 3.2 (2.9) 3.0 (3.1) 2.0 (2.9)	 3.0 (2.9) 2.8 (2.9) 2.0 (2.8)	 0.05 0.42 0.84
	Return to ED within 6-month after randomization, n/N (%)	255/872 (29.2)	231/835 (27.7)	231/816 (28.3)	0.80
	Hospital admission 6-month after ED discharge, n/N (%)	83/872 (9.5)	87/835 (10.4)	84/816 (10.3)	0.80
	Diagnostic accuracy, % (95% CI) Sensitivity Specificity	 86 (82-90) 53 (49-58)	 85 (80-89) 50 (45-54)	 84 (79-89) 53 (49-57)	 0.74 0.38
Author conclusions: *"Initial US was associated with lower cumulative radiation exposure than initial CT, without significant differences in high-risk diagnoses with complications, SAEs, pain scores, return ED visits, or hospitalizations". Pg.1100*					
CI=confidence interval; ED=emergency department; POCUS=point-of-care ultrasonography; SAE=serious adverse event; SD=standard deviation; US=ultrasonography					