ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2023 September 25; 12(4): 73-111

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Bimonthly Volume 12 Number 4 September 25, 2023

EVIDENCE REVIEW

MINIREVIEWS

SYSTEMATIC REVIEWS

World Journal of Nephrology

Bimonthly Volume 12 Number 4 September 25, 2023

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Nephrology*, Ahmed Akl, MD, FACP, FASN, ISN Educational Ambassador & Mentor, ISN Education Social Media Member, Mansoura 35516, Egypt. aiakl2001@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Nephrology* (*WJN*, *World J Nephrol*) is to provide scholars and readers from various fields of nephrology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc*.

INDEXING/ABSTRACTING

The *WJN* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Li Zuo, Ying-Yong Zhao

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-6124/editorialboard.htm

PUBLICATION DATE
September 25, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2023 September 25; 12(4): 73-81

DOI: 10.5527/wjn.v12.i4.73

ISSN 2220-6124 (online)

EVIDENCE REVIEW

Moderate stepwise restriction of potassium intake to reduce risk of hyperkalemia in chronic kidney disease: A literature review

Ali AlSahow

Specialty type: Urology and nephrology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Park JH, South Korea; Revuelta K, Spain; Zhang J

Received: March 3, 2023
Peer-review started: March 3, 2023
First decision: May 25, 2023
Revised: June 13, 2023
Accepted: June 26, 2023
Article in press: June 26, 2023
Published online: September 25, 2023

Ali AlSahow, Department of Nephrology, Jahra Hospital, Jahra 00004, Kuwait

Corresponding author: Ali AlSahow, FASN, FRCP (C), MBChB, Consultant Nephrologist, Department of Nephrology, Jahra Hospital, PO Box 2675, Jahra Central, 01028, Jahra 00004, Kuwait. alsahow@hotmail.com

Abstract

A potassium-rich diet has several cardiovascular and renal health benefits; however, it is not recommended for patients with advanced chronic kidney disease or end-stage kidney disease because of the risk of life-threatening hyperkalemia. To assess the strength of evidence supporting potassium intake restriction in chronic kidney disease, the medical literature was searched looking for the current recommended approach and for evidence in support for such an approach. There is a lack of strong evidence supporting intense restriction of dietary potassium intake. There are several ways to reduce potassium intake without depriving the patient from fruits and vegetables, such as identifying hidden sources of potassium (processed food and preservatives) and soaking or boiling food to remove potassium. An individualized and gradual reduction of dietary potassium intake in people at risk of hyperkalemia is recommended. The current potassium dietary advice in chronic kidney disease needs to be reevaluated, individualized, and gradually introduced.

Key Words: Chronic kidney disease; Potassium intake; Plant-based diet; Hyperkalemia; Potassium removal

Core Tip: A potassium-rich diet has several cardiovascular and renal health benefits; however, it is not recommended for patients with advanced chronic kidney disease or end-stage kidney disease because of the risk of life-threatening hyperkalemia. However, there is a lack of strong evidence supporting this restrictive approach. There are several ways to reduce potassium intake without depriving the patient of fruits and vegetables, such as identifying hidden sources of potassium (processed food and preservatives) and soaking or boiling food to remove potassium. An individualized and gradual reduction of dietary potassium intake in people at risk of hyperkalemia is recommended.

Citation: AlSahow A. Moderate stepwise restriction of potassium intake to reduce risk of hyperkalemia in chronic kidney disease: A literature review. *World J Nephrol* 2023; 12(4): 73-81
URL: https://www.wjgnet.com/2220-6124/full/v12/i4/73.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i4.73

INTRODUCTION

A potassium-rich diet has several cardiovascular and renal health benefits[1-4]. However, it is not recommended in patients with advanced chronic kidney disease (CKD) or end-stage kidney disease (ESKD) because of the risk of hyperkalemia[5]. In fact, restriction of dietary potassium intake is the current standard of care. Due to the lack of strong evidence supporting this approach, there are calls to reevaluate and individualize the potassium dietary advice for patients with CKD[1,2]. In this review, the current recommendations, the argument against a restrictive approach, and an individualized, gradual reduction of dietary potassium intake were discussed.

Potassium intake and health

A potassium-rich diet can help decrease blood pressure and the risk of CKD and its progression, cardiovascular disease, stroke, and mortality[1-4]. Fruits and vegetables in most diets supply the majority of dietary potassium[5]. The alkaline content of such a potassium-rich, plant-based diet may correct CKD-associated metabolic acidosis. Fiber from potassium-rich fruits and vegetables improves the lipid profile, lowers body weight, increases stool volume and frequency, improves colonic epithelium integrity reducing toxin absorption, and improves the gut microbiome reducing systemic inflammation[1-4]. The Kidney Disease Outcomes Quality Initiative 2020 nutrition guideline suggested increasing fruit and vegetable intake to help reduce weight, blood pressure, and net acid production, all of which may help lower the rate of CKD progression[6]. A plant-based diet also helps decrease the risk of calcium oxalate stone formation by increasing urinary citrate levels and reducing the calcium excretion rate[3].

The minimum daily requirement for potassium in adults, estimated based on its unavoidable loss through sweat, stool, urine, and other sources, is about 1.6 g[7]. Table 1 Lists the recommended daily intake of potassium for the general population. It is important to know that the majority of people around the world consume less than what is recommended[8-10].

Dietary potassium intake recommendations in adult patients with CKD

Patients with an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2 are generally at low risk of hyperkalemia when consuming the recommended amount of potassium for the general population, even during treatment with renin angiotensin aldosterone system (RAAS) blockers. Hyperkalemia may develop in patients receiving a high dose of RAAS blockers and/or who have a high potassium intake (> 5 g/d) in the presence of severe heart failure and/or diabetes[8]. Table 2 outlines the current potassium intake recommendations for patients with advanced CKD (stages 3b–5) and ESKD to avoid hyperkalemia. It reveals a lack of consensus regarding recommendations for a low potassium diet. A low potassium diet is defined as a dietary intake of 2-3g/d of potassium[5]. In CKD populations, potassium intake is estimated to average around 2.4 g/d[11].

Uncertainties and challenges of dietary potassium restriction in CKD

Recommendations to limit potassium intake in CKD and ESKD are standard practice for two reasons: to prevent acute hyperkalemia (when postprandial potassium absorption exceeds cellular uptake and body excretion); and to prevent chronic hyperkalemia (when potassium bioaccumulation or total body potassium exceeds cellular uptake and potassium excretion)[12]. However, this approach also restricts intake of fruits, vegetables, dairy, grains, nuts, and legumes because they are major sources of potassium[5,12-14]. This in turn deprives patients of the health benefits discussed earlier, and it may need to be reevaluated for several reasons.

There is a lack of direct evidence regarding the benefit of restricting potassium intake in CKD from randomized controlled trials[15,16]. The results from observational studies regarding the association between higher urinary potassium excretion and mortality and kidney outcomes are conflicting[4,6,15]. Dietary potassium restriction is difficult because it requires lifestyle changes that may lead to loss of enjoyment in food and impact social activities. It may result in extra financial costs for special diets[15,16]. Restriction may lower the intake of other beneficial nutrients resulting in a poor diet, which may contribute to malnutrition in advanced CKD[17] and may lead to cardiovascular disease[18].

The National Kidney Foundation defines potassium-rich food as food with more than 200 mg of potassium per serving [19]. This arbitrary threshold can be confusing. For example, tangerines are a low-potassium food while oranges are a high-potassium food, despite having relatively similar nutrient contents and densities[20]. In addition, evidence suggests that gut-kidney kaliuretic signaling initiates urinary potassium excretion before the rise in plasma potassium and independent of plasma potassium and plasma aldosterone[4], which may explain why little to no association exists between serum potassium levels and potassium intake in CKD patients[16,21-24].

An unprocessed plant-based diet rich in potassium may not always lead to hyperkalemia for several reasons. Not all fruits and vegetables are rich in potassium[1]. The 24-h urine potassium recovery from animal-based diets is about 80% and from unprocessed plant-based diets is about 50%-60%. This lower bioavailability of unprocessed plant potassium might enable CKD patients to benefit from plant-based diets without precipitating hyperkalemia[1,3,25]. Plants are the

Table 1 Recommended adequate intake of potassium for adults in the general population

Institution	K intake g/d
WHO and EFSA[32,33]	3.5
United States and Canada[34,35]	
Male	3.4
Female	2.6
Japan[7]	2.7–3.0

EFSA: European Food Safety Authority; K: Potassium; WHO: World Health Organization.

only natural source of fiber, a nondigestible, nonabsorbable carbohydrate polymer that increases stool quantity and frequency, facilitating colonic elimination of potassium and protecting against hyperkalemia[3]. Plants provide a natural alkali, which may facilitate the transfer of potassium to the intracellular compartment, especially in metabolic acidosis[1,3,5,16]. Complex carbohydrates found in fruits and vegetables increase the insulin-mediated cellular uptake of potassium, helping to lower the risk of hyperkalemia[1,3,16]. The mineral content of vegetables varies with vegetable size, weather conditions, and cultivation techniques[26]. Many dietary recommendations are based on the mineral content of raw whole foods and not chopped, cooked foods[23,27]. Restricting sodium intake and encouraging a potassium-rich, plant-based diet may help control hypertension, reducing the need for hyperkalemia-inducing antihypertensive medications, such as β-blockers. It may also allow the reduction of the dosage of RAAS blockers[2], although this approach is controversial due to the negative effects on kidney and patient survival[17,15].

Potassium restriction should also be reevaluated because guidelines do not make specific recommendations for potassium in processed food or food additives and do not discuss potassium bioavailability. Potassium additives provide almost three times the amount of potassium found in additive-free counterparts, and potassium additives in processed foods have a high bioavailability contributing to hyperkalemia[24]. Because of the pressure on the food industry to decrease sodium in processed food, but not the salty taste, potassium use has increased in low-sodium processed foods [24,28,29]. Advice to restrict sodium alone for patients who need dietary sodium and potassium restriction may inadvertently increase potassium intake if a patient unknowingly switches to low-sodium products with potassium additives[30]. Moreover, advising CKD patients to restrict potassium-rich food without proper counseling may lead them to choose sodium- and potassium-rich processed foods over healthier alternatives[30]. Potassium-based food additives are found in precooked or shelf-stable foods, powdered dressings, sauces, preserved meats, stuffed pasta, jellies, concentrated fruit juices, processed cheeses, and margarine[5]. A list of potassium-based food additives is available elsewhere [31].

There are pitfalls associated with the tools used to estimate dietary intake of potassium. Plasma potassium levels are usually measured before hemodialysis and in a fasting state for non-hemodialysis (not a postprandial state). This timing is better suited to evaluate chronic hyperkalemia risk but not to detect acute postprandial hyperkalemia[30]. The standard assessment method is a 24-h urine collection, which assumes that 24-h urinary potassium excretion always reflects 70% of ingested potassium. However, collection errors may lead to incorrect assumptions and advice[28]. In addition, a single collection cannot accurately estimate potassium intake due to day-to-day variability in intake, gastrointestinal excretion, which is higher at low eGFR, and cell distribution. Spot urine should not be used to estimate intake at an individual level [11,15].

Non-urinary-based dietary assessment tools (food frequency questionnaires, diet records, and 24-h diet recalls) are not affected by changes in potassium homeostasis in CKD but rely on food databases. Thus, database inaccuracies (*e.g.*, differences in nutrients between processed, restaurant-cooked, and home-cooked foods) can lead to measurement errors [11,15].

Food frequency questionnaires record the consumption frequency of a predefined list of foods and beverages over weeks or months. It is the most cost-effective and time-saving method with a low burden, but errors occur due to recall bias (*i.e.*, respondents not correctly memorizing intake) and when questionnaires are not relevant to local dietary habits or seasonal changes. Furthermore, they may not account for potassium additives and substitutes and cooking methods[11,15].

Diet recall documents all foods and beverages consumed in the previous 1-7 d with moderate precision, cost, time, and burden. However, the method is prone to recall bias and underreporting, especially in overweight individuals. Precision is acceptable because quantities of consumed foods are defined, including potassium additives and cooking methods. However, more detailed intake information increases data collection complexity[11,15].

Diet records are prospective documentation of intake with minimal recall bias, and it is the most accurate if foods are documented and weighed correctly. However, it is costly and time consuming. Respondents may simplify or underreport complicated meals or even alter eating behaviors choosing healthier foods (selective reporting). Keeping records for more than 4 d may lead to inaccurate results due to respondent fatigue. It is also less suitable for CKD patients, in whom limited health literacy and cognitive impairment are common[11,15].

A gradual, individualized approach

A stepwise reduction in potassium intake is advised to ensure a balanced intake of fresh fruits and vegetables and fiber

Table 2 Recommended potassium intake for adult patients with chronic kidney disease

Source	Advice
KDOQI	
2000[36]	CKD 1-5 ND: Unrestricted intake unless serum potassium level is elevated; HD: Intake up to 2.7-3.1 g/d; PD: Intake close to 3-4 g/d
2004[18]	CKD 1-2: intake > 4 g/d; CKD 3-4: intake 2-4 g/d
2020[6]; with the Academy of Nutrition and Dietetics	Statement 3.3.2: in adults with CKD 1–4, we suggest that prescribing increased fruit and vegetable intake may decrease body weight, blood pressure, and net acid production (2C); Statement 6.1.1: in adults with CKD 1–4, we suggest reducing net acid production through increased dietary intake of fruits and vegetables (2C) to reduce the rate of decline of residual kidney function; Statement 6.4: Adjust dietary potassium intake to maintain serum potassium within the normal range for adults with CKD 3–5D (opinion)
2019[19]; NKF educational website	A potassium restricted diet is typically about 2 g/d. A physician or dietitian will advise patient on the specific level of restriction needed based on individual health
EBPG	
2007[37]	Recommendation of 4.2 g/d; in patients with pre-dialysis serum potassium greater than 6 mmol/L, a daily intake of potassium of 1950–2730 mg or 1 mmol/kg IBW is recommended
Spanish Society of Nephrology	
2008[38]	A low-potassium diet (1.5–2.0 g/d) is recommended for GFR < 20 mL/min or GFR < 50 mL/min if potassium-increasing drugs are taken
Academy of Nutrition and Dietetics	
2010[39]	Daily potassium intake of less than 2.4 g for CKD stages 3-5 who exhibit hyperkalemia
2014[40]	CKD stages 3-5 not on dialysis: no restriction until hyperkalemia is present, then individualized; HD: 2-4 g/d or 40 mg/kg of BW/d; PD: individualized to achieve normal serum levels
Australian guidelines	
2005[41]	Reduced potassium diet should commence when serum potassium in pre-dialysis patients is > 5.5 mmol/L (Opinion). A reduced potassium diet limits the 24-h intake to about 3.1 mg
2013[42]	Early CKD patients with persistent hyperkalemia restrict their dietary potassium intake with the assistance of an appropriately qualified dietitian (2D)
Italian Society of Nephrology	
2019[43]	Statement 1.2: serum potassium ≥ 5 mmol/L must be considered pathologic in CKD; Statement 1.3: restriction of potassium intake for non-dialysis CKD of mild-to-moderate degree is not recommended unless potassium levels are above 5 mmol/L in the absence of any other apparent cause. Then, it is recommended to limit food with high potassium content, especially if low in fiber, and pretreat (soaking and boiling) before cooking to remove potassium; Statement 2.3: restrict potassium intake to 2-3 g/d for advanced CKD and HD patients
Renal Association	
2020[17]	A low potassium diet should be instituted for patients with advanced CKD and ESKD with persistent hyperkalemia with serum potassium > 5.5 mmol/L; a low potassium diet is defined by a dietary intake of 2-3 g/d
Cupisti *et al*[5]	Limit intake to 2.5-3.0 g/d or 1 mmol/kg/IBW for mild hyperkalemia of 5.0-5.5 mmol/L; limit intake to 2.0-2.5 g/d for moderate hyperkalemia of 5.5-6.0 mmol/L; 1.5-2.0 g/d for severe hyperkalemia of 6.0-6.5 mmol/L
Yamada *et al*[7]	Limit intake to ≤ 2 g/d for eGFR ≥ 30 and ≤ 1.5 g/d for eGFR < 30; limit intake to ≤ 2 g/d for HD and 2.0-2.5 g/d for PD
Kalantar-Zadeh *et al*[44]	Recommended potassium intake is the same as for the general population: (1) eGFR ≥ 60 mL/minute/1.73 m^2 without substantial proteinuria (< 0.3 g of protein/d) but high risk for CKD because of DM, HTN, PCKD, or a solitary kidney, *etc*; or (2) eGFR of 30-59 mL/minute/1.73 m^2 without substantial proteinuria (unless frequent or severe hyperkalemia episodes are likely); Limit potassium intake to < 3 g/d: (1) eGFR < 30 mL/minute/1.73 m^2 if hyperkalemia occurs frequently during high-fiber intake; (2) Any eGFR if there is substantial proteinuria and frequent hyperkalemia during high-fiber intake; (3) Patients with good residual kidney function transitioning to dialysis if hyperkalemia occurs frequently during high-fiber intake; or (4) Dialysis patients or patients at any stage with existing or imminent protein-energy wasting defined according to the International Society of Renal Nutrition and Metabolism criteria
Clegg *et al*[13]	Limit potassium intake to 3 g/d

BW: Body weight; CKD: Chronic kidney disease; DM: Diabetes mellitus; EBPG: European Best Practice Guidelines; eGFR: Estimated glomerular filtration rate; ESKD: End-stage kidney disease; GFR: Glomerular filtration rate; HD: Hemodialysis; HTN: Hypertension; IBW: Ideal body weight; KDOQI: Kidney Disease Outcomes Quality Initiative; ND: Not on dialysis; NKF: National Kidney Foundation; PCKD: Polycystic kidney disease; PD: Peritoneal dialysis.

Table 3 Strategies to reduce the risk of hyperkalemia in chronic kidney disease before employing potassium dietary restriction

Strategy
Calculate the eGFR to assess the patient's risk of hyperkalemia
Avoid hidden sources, especially potassium-based additives in processed food and salt substitutes in low-sodium processed food
Increase stool frequency to increase the proportion of potassium excreted by the gut
Identify and correct non-dietary factors that influence serum potassium levels to keep potassium within normal range: (1) Drugs that may elevate serum potassium that can and should be discontinued/avoided (NSAIDs, COX-2 inhibitors, PPIs, potassium supplements, herbal remedies); (2) Inorganic metabolic acidosis associated with advanced CKD when serum bicarbonate level < 22 mmol/L; (3) Uncontrolled DM. Insulin deficit and/or hyperglycemic hyperosmolality lower acute potassium load movement into cells; and (4) Other causes that may directly or indirectly increase potassium level include volume depletion, adrenal insufficiency, catabolic state (major cell damage, hemolysis) and GI problems (diarrhea, constipation, bleeding)
Reduce the dose of medications known to elevate serum potassium level if in use or switch to an alternative if possible: RAASi (DRA, ACEI, ARB, MRA, ARNI, ASI), β-Blockers, potassium-sparing diuretics (Amiloride, Triamterene), calcineurin inhibitors (cyclosporine, tacrolimus), digoxin, heparin, trimethoprim/co-trimoxazole
Use diuretics. The effect depends on eGFR. Dialysis patients with reasonable residual kidney function may respond to loop diuretics. Diuretics work best when diuresis is desired, or an additional antihypertensive agent is considered
Implement sick-day rules by advising patients on the risk of AKI and hyperkalemia during acute illness and on measures to avoid them. However, it can be difficult and counterproductive
Improve potassium removal in hemodialysis (thrice weekly, 4-h sessions), which is mainly by diffusion: (1) Increase session duration and frequency, increase blood and dialysate flow, increase filter surface area, correct vascular access status recirculation, and use lower dialysate potassium; (2) Higher dialysate glucose concentration triggers insulin release, which enhances cellular uptake of potassium; (3) Higher bicarbonate bath concentration increases blood pH, which enhances cellular uptake of potassium; (4) Minimize pre-dialysis exposure to drugs that increase cellular uptake of potassium such as insulin and β_2-agonist inhalers because they reduce pre-dialysis potassium, which reduces dialytic removal and exacerbates potassium rebound post-dialysis
Use one of the newer generation potassium binders (patiromer or sodium zirconium cyclosilicate). However, they primarily target chronic hyperkalemia not acute postprandial hyperkalemia and may increase pill burden

Information compiled from references[1,3,5,13,15-17,45-51]. ACEI: Angiotensin converting enzyme inhibitor; AKI: Acute kidney injury ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor/neprilysin inhibitor; ASI: Aldosterone synthase inhibitor; CKD: Chronic kidney disease; COX-2: Cyclooxygenase 2; DM: Diabetes mellitus; DRA: Direct renin antagonist; eGFR: Estimated glomerular filtration rate; GI: Gastrointestinal; MRA: Mineralocorticoid receptor antagonist; NSAID: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; RAASi: Renin angiotensin aldosterone system inhibitors.

Table 4 Strategies to gradually introduce a mild potassium-restrictive dietary plan

Strategy	Steps
Ensure care is patient centered	(1) Involve dietitians, nurses, psychologists, pharmacists, and social workers if resources allow to ensure patient understanding. Clarify roles and responsibilities of each regarding dietary education to reduce conflicting information and deliver nutrition training to non-dietetic staff to promote consistency of message; (2) Individualize the plan according to patient's lifestyle, and personal, religious, and sociocultural background. Train staff, particularly dietitians, to ensure expertise on culturally important foods and dietary patterns; (3) Explain the plan's benefits and limitations and give the patient ample time to accept, to change dietary habits, and to adhere. Plant-based diets can be eco-friendly and economically advantageous. These arguments may promote adherence; (4) Adapt to all levels of education. Health literacy improves patient access and use of health information. Many patients have low health literacy, which may hinder communication, comprehension, and use of digital technology, prolonging the time to convey the message; (5) Identify vulnerable patients (young, socially isolated) who may need more nutritional education and support; and (6) Provide early and continuous access to the renal dietitian for collaboration on plan design and implementation
Instruct patients to identify potassium content of foods to avoid potassium-rich food. Food with > 200 mg of potassium/serving is defined as a potassium-rich food by the National Kidney Foundation	(1) Check serving size/weight. A large low-potassium food serving may have more potassium than a small high-potassium food serving; (2) Spread potassium-rich food items throughout the day to avoid acute postprandial hyperkalemia; (3) Increase the intake of low-potassium to fiber ratio fruits (apple, apricot, berries) and vegetables (green beans, peas, asparagus, lettuce, onions) and reduce the intake of high-potassium to fiber ratio food (processed juice and sauces); (4) Avoid food items that are very rich in potassium, such as edamame, molasses, and white and black beans; (5) Switch to soy-, rice-, and almond-based milk and yogurt because they may have less potassium and phosphorus than dairy; and (6) Avoid 93% lean ground beef since it has substantially more protein, phosphorus, and potassium than 70% lean ground beef
Describe food preparation methods and cooking procedures that may help reduce the potassium content of food	See Table 5
Apply dietary plan to real life	(1) Invite and engage both patients and family members responsible for buying and preparing food (spouse, relative) in the appointments with the dietitian to translate dietary recommendations into accessible plans; (2) Adopt a stepwise approach allowing patients to adapt to dietary recommendations gradually. Patients do not eat calories, protein, or carbohydrates; they eat food, therefore, translate information about nutrients into food using food models, pictures, and recipes to make dietary counseling real and achievable; (3) Simplify nutrition

	education/advice particularly for those with multiple dietary needs. Avoid weighing or counting servings if possible so it is more practical for most patients. Use the hand to estimate serving size; (4) Explore unrestricted food. Discussion should focus less on what is not allowed and more about what is. Counseling based on food habits highlights foods that should be avoided with alternatives for replacement. For example, animal-based food (cow's milk) may be replaced by plant-based food (vegetable milk such as soy, almond, and coconut); (5) Nothing should be "forever." Social life is shared around a table; more restaurants have plant-based options, but the main courses in family meetings are often animal-based. Patients will not easily give up food they love. Allowing occasional freedom can improve long-term adherence; (6) Suggest cooking classes for recipes desired by patients to stimulate emotional involvement. Explore seasonal fruits and vegetables; (7) Offer positive feedback for the patient/caregiver during visits to motivate the patient to continue with the plan. Show how it affects laboratory values, intradialytic weight over time, or even number of pills patient is taking; (8) Meal delivery service may benefit patients who live alone or have difficulty shopping and preparing meals; and (9) Utilize the internet and social media: (a) Smartphones and tablets help interactive sessions (sharing pictures of dishes, describing sizes and preparation methods); (b) Telehealth/virtual nutrition counseling supports patients who need frequent reinforcement that outpatient clinic timing does not allow for or for those who have difficulty attending in-person clinical settings. They are cost effective in communities where long distances represent a barrier to face-to-face nutritional education; (c) Dietitian-facilitated and -supervised online peer support programs can promote healthful dietary behaviors. Age and cultural appropriateness of group participants should be considered; and (d) Online resources and technology-based interventions using smart phones (E-learning) can be used as platform for teaching and workshops reinforcing nutrition education and self-management plans

Information compiled from references[1,2,5,12,15,16,19,20,31,45-50,52].

Table 5 Food preparation methods to help lower food contents of potassium and ease restriction intensity

Strategy	Tips
Wash and peel the fruit and vegetable skin to lower potassium content then chop into small pieces. Peeling reduces fiber content	
Place in cold water so they do not darken, then rinse in warm water for a few seconds	
Soak for at least 4 h in warm water, then rinse, change the water, and soak for another 12 h (longer for legumes)	(1) Use ten times the amount of water to the amount of fruits or vegetables; (2) Water may need to be changed every 4 h for potassium-rich items; (3) Legumes may need to be soaked for 36 h at a ratio of 100 g per 1.5 L water with frequent changing of water; (4) Soaking lowers potassium more efficiently in water-rich soft foods like tomatoes and apples compared to potatoes or chocolate; (5) Soaking fresh potatoes, canned potatoes, and frozen fries alone without cooking afterward is ineffective in removing potassium; (6) Soaking alone is also ineffective for potassium removal from bananas, but boiling improves its removal; and (7) Soaking after normal cooking may increase potassium removal
Rinse afterwards under warm water for a few seconds before eating or cooking	
Cook vegetables with five times as much water as vegetables	(1) Vegetables can be boiled in conventional cookware, a pressure cookware/autoclave, or microwave oven; (2) Potassium-rich items may need to be boiled twice. The double cooking technique; (3) Potassium removal by cooking shredded potatoes exceeds that of cooking cubed potatoes; (4) Adequate soaking followed be cooking may allow legume consumption twice weekly. Soaking dried legumes alone is ineffective for potassium removal; cooking after soaking significantly reduces potassium content. Cook in water at a ratio of 100 g per 1.5 L water (3 L water for dried chickpeas due to the long cooking duration they need). Canned legumes, drained and rinsed, contain less potassium and phosphorus than dried legumes, and the final contents after soaking and normal cooking make them a better alternative to the laborious preparation method for dried legumes. However, precooked legumes often contain salt and/or salt substitutes; (5) Freezing of green beans/chard (home frozen and industrial frozen) alone does not reduce potassium content. However, it leads to greater reduction of potassium contents when followed by soaking than soaking fresh ones. Cooking without soaking reduces potassium content less than cooking of soaked frozen ones. Soaking plus cooking is superior to either soaking alone or cooking without soaking alone for fresh green beans / chard; (6) Cooking methods that avoid contact with water (dry heat cooking, steam cooking, dehydration cooking) remove less potassium; and (7) Aromatic herbs can improve food taste and palatability reduced by peeling and boiling

Information compiled from references[6,19,20,52-60].

by patients with advanced CKD who are not prone to hyperkalemia[5,16]. Table 3 summarizes several strategies that should be implemented to minimize the risk of hyperkalemia before restricting potassium intake. Table 4 describes the steps to gradually restrict potassium intake and to minimize the impact of this approach on the patient. Table 5 describes cooking methods that can help reduce potassium levels in fruits and vegetables to increase the number of permissible food items.

CONCLUSION

Although potassium intake restriction is the standard of care in advanced CKD and ESKD, there is a need for the reevaluation of this approach in CKD patients who do not have hyperkalemia. There are health benefits of a plant-based, potassium-rich diet, and it is difficult to implement a low-potassium diet. There is scarce and inconsistent data attributed to dietary potassium in patients with CKD, and the risk of hyperkalemia may have been overstated. Under the supervision of a skilled dietician, the list of permissible food items may be gradually expanded by introducing unprocessed and properly prepared plant-based foods, especially those with a low potassium to fiber ratio, to improve the quality of food intake. Further research on moderate gradual liberalization of potassium intake in patients with CKD is certainly warranted.

FOOTNOTES

Author contributions: The sole author of the manuscript.

Conflict-of-interest statement: There are no conflicts of interest to report.

Country/Territory of origin: Kuwait

ORCID number: Ali AlSahow 0000-0001-8081-3244.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Carrero JJ**, González-Ortiz A, Avesani CM, Bakker SJL, Bellizzi V, Chauveau P, Clase CM, Cupisti A, Espinosa-Cuevas A, Molina P, Moreau K, Piccoli GB, Post A, Sezer S, Fouque D. Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol* 2020; **16**: 525-542 [PMID: 32528189 DOI: 10.1038/s41581-020-0297-2]

2 **Joshi S**, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. *Am J Kidney Dis* 2021; **77**: 287-296 [PMID: 33075387 DOI: 10.1053/j.ajkd.2020.10.003]

3 **Palmer BF**, Colbert G, Clegg DJ. Potassium Homeostasis, Chronic Kidney Disease, and the Plant-Enriched Diets. *Kidney360* 2020; **1**: 65-71 [PMID: 35372861 DOI: 10.34067/KID.0000222019]

4 **Wei KY**, Gritter M, Vogt L, de Borst MH, Rotmans JI, Hoorn EJ. Dietary potassium and the kidney: lifesaving physiology. *Clin Kidney J* 2020; **13**: 952-968 [PMID: 33391739 DOI: 10.1093/ckj/sfaa157]

5 **Cupisti A**, Kovesdy CP, D'Alessandro C, Kalantar-Zadeh K. Dietary Approach to Recurrent or Chronic Hyperkalaemia in Patients with Decreased Kidney Function. *Nutrients* 2018; **10** [PMID: 29495340 DOI: 10.3390/nu10030261]

6 **Ikizler TA**, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, Kaysen GA, Kopple JD, Teta D, Yee-Moon Wang A, Cuppari L. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis* 2020; **76**: S1-S107 [PMID: 32829751 DOI: 10.1053/j.ajkd.2020.05.006]

7 **Yamada S**, Inaba M. Potassium Metabolism and Management in Patients with CKD. *Nutrients* 2021; **13** [PMID: 34063969 DOI: 10.3390/nu13061751]

8 **Burnier M**. Should we eat more potassium to better control blood pressure in hypertension? *Nephrol Dial Transplant* 2019; **34**: 184-193 [PMID: 29301002 DOI: 10.1093/ndt/gfx340]

9 **United States Department of Agriculture**. National Health and Nutrition Examination Survey: What we eat in America. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/usual/Usual_Intake_gender_WWEIA_2013_2016.pdf

10 **Jarrar AH**, Stojanovska L, Apostolopoulos V, Cheikh Ismail L, Feehan J, Ohuma EO, Ahmad AZ, Alnoaimi AA, Al Khaili LS, Allowch NH, Meqbaali FTA, Souka U, Al Dhaheri AS. Assessment of Sodium Knowledge and Urinary Sodium Excretion among Regions of the United Arab Emirates: A Cross-Sectional Study. *Nutrients* 2020; **12** [PMID: 32916952 DOI: 10.3390/nu12092747]

11 **Ginos BNR**, Engberink RHGO. Estimation of Sodium and Potassium Intake: Current Limitations and Future Perspectives. *Nutrients* 2020; **12** [PMID: 33114577 DOI: 10.3390/nu12113275]

12 **St-Jules DE**, Clegg DJ, Palmer BF, Carrero JJ. Can Novel Potassium Binders Liberate People with Chronic Kidney Disease from the Low-Potassium Diet? A Cautionary Tale. *Clin J Am Soc Nephrol* 2022; **17**: 467-472 [PMID: 34670798 DOI: 10.2215/CJN.09660721]

13 **Clegg DJ**, Headley SA, Germain MJ. Impact of Dietary Potassium Restrictions in CKD on Clinical Outcomes: Benefits of a Plant-Based Diet. *Kidney Med* 2020; **2**: 476-487 [PMID: 32775988 DOI: 10.1016/j.xkme.2020.04.007]

14 **Cases A**, Cigarrán-Guldrís S, Mas S, Gonzalez-Parra E. Vegetable-Based Diets for Chronic Kidney Disease? It Is Time to Reconsider. *Nutrients* 2019; **11** [PMID: 31167346 DOI: 10.3390/nu11061263]

15 **Clase CM**, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF,

Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R; Conference Participants. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2020; **97**: 42-61 [PMID: 31706619 DOI: 10.1016/j.kint.2019.09.018]

16 **Fishbane S**, Charytan DM, Chertow GM, Ford M, Kovesdy CP, Pergola PE, Pollock C, Spinowitz B. Consensus-Based Recommendations for the Management of Hyperkalemia in the Hemodialysis Setting. *J Ren Nutr* 2022; **32**: e1-e14 [PMID: 34364782 DOI: 10.1053/j.jrn.2021.06.003]

17 **Alfonzo A**, Harrison A, Baines R, Chu A, Mann S, MacRury M. Renal Association Clinical Practice Guidelines - Treatment of Acute Hyperkalemia in Adults. 2020 July. Available from: https://ukkidney.org/health-professionals/guidelines/treatment-acute-hyperkalaemia-adults

18 **Kidney Disease Outcomes Quality Initiative (K/DOQI)**. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; **43**: S1-290 [PMID: 15114537]

19 **National Kidney Foundation**. A to Z health guide: Potassium and your CKD diet. Available from: https://www.kidney.org/atoz/content/potassium

20 **St-Jules DE**, Goldfarb DS, Pompeii ML, Liebman SE, Sherman RA. Assessment and misassessment of potassium, phosphorus, and protein in the hemodialysis diet. *Semin Dial* 2018; **31**: 479-486 [PMID: 29813179 DOI: 10.1111/sdi.12713]

21 **St-Jules DE**, Goldfarb DS, Sevick MA. Nutrient Non-equivalence: Does Restricting High-Potassium Plant Foods Help to Prevent Hyperkalemia in Hemodialysis Patients? *J Ren Nutr* 2016; **26**: 282-287 [PMID: 26975777 DOI: 10.1053/j.jrn.2016.02.005]

22 **Noori N**, Kalantar-Zadeh K, Kovesdy CP, Murali SB, Bross R, Nissenson AR, Kopple JD. Dietary potassium intake and mortality in long-term hemodialysis patients. *Am J Kidney Dis* 2010; **56**: 338-347 [PMID: 20580474 DOI: 10.1053/j.ajkd.2010.03.022]

23 **Ramos CI**, González-Ortiz A, Espinosa-Cuevas A, Avesani CM, Carrero JJ, Cuppari L. Does dietary potassium intake associate with hyperkalemia in patients with chronic kidney disease? *Nephrol Dial Transplant* 2021; **36**: 2049-2057 [PMID: 33247727 DOI: 10.1093/ndt/gfaa232]

24 **Picard K**. Potassium Additives and Bioavailability: Are We Missing Something in Hyperkalemia Management? *J Ren Nutr* 2019; **29**: 350-353 [PMID: 30579674 DOI: 10.1053/j.jrn.2018.10.003]

25 **Naismith DJ**, Braschi A. An investigation into the bioaccessibility of potassium in unprocessed fruits and vegetables. *Int J Food Sci Nutr* 2008; **59**: 438-450 [PMID: 18636367 DOI: 10.1080/09637480701690519]

26 **Martínez-Pineda M**, Yagüe-Ruiz C, Vercet-Tormo A. Is It Possible to Include Potato in the Diet of Chronic Kidney Disease Patients? New Culinary Alternatives for Limiting Potassium Content. *J Ren Nutr* 2020; **30**: 251-260 [PMID: 31444038 DOI: 10.1053/j.jrn.2019.07.001]

27 U.S. Department of agriculture. FoodData Central. Available from: https://fdc.nal.usda.gov/fdc-app.html#/?component=1092

28 **van Buren L**, Dötsch-Klerk M, Seewi G, Newson RS. Dietary Impact of Adding Potassium Chloride to Foods as a Sodium Reduction Technique. *Nutrients* 2016; **8**: 235 [PMID: 27110818 DOI: 10.3390/nu8040235]

29 **Parpia AS**, Goldstein MB, Arcand J, Cho F, L'Abbé MR, Darling PB. Sodium-Reduced Meat and Poultry Products Contain a Significant Amount of Potassium from Food Additives. *J Acad Nutr Diet* 2018; **118**: 878-885 [PMID: 29311039 DOI: 10.1016/j.jand.2017.10.025]

30 **Picard K**, Mager D, Richard C. How Food Processing Impacts Hyperkalemia and Hyperphosphatemia Management in Chronic Kidney Disease. *Can J Diet Pract Res* 2020; **81**: 132-136 [PMID: 32072822 DOI: 10.3148/cjdpr-2020-003]

31 **Martínez-Pineda M**, Vercet A, Yagüe-Ruiz C. Are Food Additives a Really Problematic Hidden Source of Potassium for Chronic Kidney Disease Patients? *Nutrients* 2021; **13** [PMID: 34684570 DOI: 10.3390/nu13103569]

32 **World Health Organization**. Guideline: Potassium Intake for Adults and Children. 2012 [PMID: 23617019]

33 **Turck D**, Bresson JL, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M Hirsch-Ernst KI, Mangelsdorf I, McArdle H, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Loveren HV, Vinceti M, Willatts P Aggett P, Martin A, Przyrembel H, Brönstrup A, Ciok J, Gómez Ruiz JÁ, Sesmaisons-Lecarré A, Naska A. Dietary reference values for potassium. *EFSA J* 2016; **14**: 4592 [DOI: 10.2903/j.efsa.2016.4592]

34 **National Academies of Sciences Engineering, and Medicine**. Health and Medicine Division; Food and Nutrition Board; Committee to Review the Dietary Reference Intakes for Sodium and Potassium. Dietary Reference Intakes for Sodium and Potassium. Oria M, Harrison M, Stallings VA, editors. Washington (DC): National Academies Press (US); 2019 Mar 5 [PMID: 30844154]

35 Health Canada. Government of Canada. [Accessed 28/6/2021]. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/public-involvement-partnerships/notice-proposal-update-nutrition-labelling-table-daily-values/document.html

36 Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am J Kidney Dis* 2000; **35**: S17-S104 [PMID: 10895784 DOI: 10.1053/ajkd.2000.v35.aajkd03517]

37 **Fouque D**, Vennegoor M, ter Wee P, Wanner C, Basci A, Canaud B, Haage P, Konner K, Kooman J, Martin-Malo A, Pedrini L, Pizzarelli F, Tattersall J, Tordoir J, Vanholder R. EBPG guideline on nutrition. *Nephrol Dial Transplant* 2007; **22** Suppl 2: ii45-ii87 [PMID: 17507426 DOI: 10.1093/ndt/gfm020]

38 **Alcázar Arroyo R**. [Electrolyte and acid-base balance disorders in advanced chronic kidney disease]. *Nefrologia* 2008; **28** Suppl 3: 87-93 [PMID: 19018744]

39 **Academy of Nutrition and Dietetics**. 2010 Chronic Kidney Disease (CKD) Evidence-based nutrition practice guideline. Available from: https://www.andeal.org/topic.cfm?cat=3927

40 **Beto JA**, Ramirez WE, Bansal VK. Medical nutrition therapy in adults with chronic kidney disease: integrating evidence and consensus into practice for the generalist registered dietitian nutritionist. J Acad Nutr Diet. 2014 Jul;114(7):1077–87. [PMID: 24582998 DOI: 10.1016/j.jand.2013.12.009]

41 **Pollock C**, Voss D, Hodson E, Crompton C; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Nutrition and growth in kidney disease. *Nephrology (Carlton)* 2005; **10** Suppl 5: S177-S230 [PMID: 16371087 DOI: 10.1111/j.1440-1797.2005.00506_1.x]

42 **Johnson DW**, Atai E, Chan M, Phoon RK, Scott C, Toussaint ND, Turner GL, Usherwood T, Wiggins KJ; KHA-CARI. KHA-CARI guideline: Early chronic kidney disease: detection, prevention and management. *Nephrology (Carlton)* 2013; **18**: 340-350 [PMID: 23506545 DOI: 10.1111/nep.12052]

43 **Bianchi S**, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. *J Nephrol* 2019; **32**: 499-516 [PMID: 31119681 DOI: 10.1007/s40620-019-00617-y]

44 **Kalantar-Zadeh K**, Fouque D. Nutritional Management of Chronic Kidney Disease. *N Engl J Med* 2017; **377**: 1765-1776 [PMID: 29091561 DOI: 10.1056/NEJMra1700312]

45 **Palmer BF**, Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019. *Am J Kidney Dis* 2019; **74**: 682-695 [PMID: 31227226 DOI: 10.1053/j.ajkd.2019.03.427]

46 **Pirklbauer M**. Hemodialysis treatment in patients with severe electrolyte disorders: Management of hyperkalemia and hyponatremia. *Hemodial Int* 2020; **24**: 282-289 [PMID: 32436307 DOI: 10.1111/hdi.12845]

47 **Bansal S**, Pergola PE. Current Management of Hyperkalemia in Patients on Dialysis. *Kidney Int Rep* 2020; **5**: 779-789 [PMID: 32518860 DOI: 10.1016/j.ekir.2020.02.1028]

48 **Cupisti A**, Avesani CM, D'Alessandro C, Garibotto G. Nutritional management of kidney diseases: an unmet need in patient care. *J Nephrol* 2020; **33**: 895-897 [PMID: 32785842 DOI: 10.1007/s40620-020-00829-7]

49 **Stevenson J**, Tong A, Gutman T, Campbell KL, Craig JC, Brown MA, Lee VW. Experiences and Perspectives of Dietary Management Among Patients on Hemodialysis: An Interview Study. *J Ren Nutr* 2018; **28**: 411-421 [PMID: 29691161 DOI: 10.1053/j.jrn.2018.02.005]

50 **Ghazi L**. Sick day protocol to prevent AKI: What is the Evidence? Renal Fellow Network. Available from: https://www.renalfellow.org/2021/06/06/sick-day-protocol-to-prevent-aki-what-is-the-evidence/

51 **Hung AM**, Hakim RM. Dialysate and serum potassium in hemodialysis. *Am J Kidney Dis* 2015; **66**: 125-132 [PMID: 25828570 DOI: 10.1053/j.ajkd.2015.02.322]

52 **University of Minnesota Extension: Real life, good food**. Available from: https://reallifegoodfood.umn.edu/eat/nutrition/portion-size

53 **Picq C**, Asplanato M, Bernillon N, Fabre C, Roubeix M, Ricort JM. Effects of water soaking and/or sodium polystyrene sulfonate addition on potassium content of foods. *Int J Food Sci Nutr* 2014; **65**: 673-677 [PMID: 24720622 DOI: 10.3109/09637486.2014.908172]

54 **Batista RAB**, Japur CC, Prestes IV, Fortunato Silva J, Cavanha M, das Graças Pena G. Potassium reduction in food by preparation technique for the dietetic management of patients with chronic kidney disease: a review. *J Hum Nutr Diet* 2021; **34**: 736-746 [PMID: 33497513 DOI: 10.1111/jhn.12846]

55 **Botanical Online: How to eliminate potassium in food**. Available from: https://www.botanical-online.com/en/food/how-eliminate-potassium-food

56 **Bethke PC**, Jansky SH. The effects of boiling and leaching on the content of potassium and other minerals in potatoes. *J Food Sci* 2008; **73**: H80-H85 [PMID: 18576999 DOI: 10.1111/j.1750-3841.2008.00782.x]

57 **Asiimwe J**, Sembajwe LF, Senoga A, Bakiika E, Muwonge H, Kalyesubula R. Overnight soaking or boiling of "Matooke" to reduce potassium content for patients with chronic kidney disease: does it really work? *Afr Health Sci* 2013; **13**: 546-550 [PMID: 24250286 DOI: 10.4314/ahs.v13i3.2]

58 **Burrowes JD**, Ramer NJ. Removal of potassium from tuberous root vegetables by leaching. *J Ren Nutr* 2006; **16**: 304-311 [PMID: 17046614 DOI: 10.1053/j.jrn.2006.07.012]

59 **Martínez-Pineda M**, Yagüe-Ruiz C, Caverni-Muñoz A, Vercet-Tormo A. Cooking Legumes: A Way for Their Inclusion in the Renal Patient Diet. *J Ren Nutr* 2019; **29**: 118-125 [PMID: 30322788 DOI: 10.1053/j.jrn.2018.08.001]

60 **Martínez-Pineda M**, Yagüe-Ruiz C, Caverni-Muñoz A, Vercet-Tormo A. Reduction of potassium content of green bean pods and chard by culinary processing. Tools for chronic kidney disease. *Nefrologia* 2016; **36**: 427-432 [PMID: 27207820 DOI: 10.1016/j.nefro.2016.03.022]

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2023 September 25; 12(4): 82-92

DOI: 10.5527/wjn.v12.i4.82

ISSN 2220-6124 (online)

MINIREVIEWS

Immunoglobulin A vasculitis nephritis: Current understanding of pathogenesis and treatment

Michela Amatruda, Nicolina Stefania Carucci, Roberto Chimenz, Giovanni Conti

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Koukoulaki M, Greece; Miao MS, China; Wang T, China

Received: February 16, 2023
Peer-review started: February 16, 2023
First decision: April 13, 2023
Revised: May 16, 2023
Accepted: June 12, 2023
Article in press: June 12, 2023
Published online: September 25, 2023

Michela Amatruda, Nicolina Stefania Carucci, Roberto Chimenz, Giovanni Conti, Pediatric Nephrology and Rheumatology Unit, AOU G Martino, University of Messina, Messina 98125, Italy

Corresponding author: Giovanni Conti, MD, Doctor, Pediatric Nephrology and Rheumatology Unit, AOU G Martino, University of Messina, Via C Valeria 1, Messina 98125, Italy. giovanniconti@hotmail.com

Abstract

The clinical spectrum of immunoglobulin A vasculitis nephritis (IgAVN) ranges from the relatively common transitory microscopic hematuria and/or low-grade proteinuria to nephritic or nephrotic syndrome, rapidly progressive glomerulonephritis, or even renal failure. Clinical and experimental studies have shown a multifactor pathogenesis: Infection triggers, impaired glycosylation of IgA1, complement activation, Toll-like-receptor activation and B cell proliferation. This knowledge can identify IgAVN patients at a greater risk for adverse outcome and increase the evidence for treatment recommendations.

Key Words: Immunoglobulin A vasculitis nephritis; Immunoglobulin A vasculitis; Henoch-Schoenlein purpura; Immunoglobulin A nephropathy; Vasculitis, glomerulonephritis

Core Tip: This review summarizes the main mechanisms involved in the pathogenesis of immunoglobulin A vasculitis nephritis and the recent treatment development, in order to decrease the risk of kidney disease progression.

Citation: Amatruda M, Carucci NS, Chimenz R, Conti G. Immunoglobulin A vasculitis nephritis: Current understanding of pathogenesis and treatment. *World J Nephrol* 2023; 12(4): 82-92
URL: https://www.wjgnet.com/2220-6124/full/v12/i4/82.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i4.82

INTRODUCTION

Immunoglobulin A (IgA) vasculitis (IgAV), also known as Henoch-Schoenlein purpura (HSP), is the most common systemic vasculitis in children. It is defined by the presence of non-thrombocytopenic palpable purpura or petechiae (mandatory criterion) predominantly located in the lower limbs, plus abdominal pain or IgA deposition in tissue biopsy or arthritis/arthralgia or renal disease[1,2]. 20%-80% of patients with IgAV develop renal involvement, termed IgAV nephritis (IgAVN), which is the key element in affecting long-term outcome[3-5].

According to the European SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) plane[6], all IgAV patients should be investigated for renal involvement at diagnosis and throughout follow-up by measuring blood pressure, determining the presence of haematuria, quantifying albuminuria and/or proteinuria and, finally, estimating glomerular filtration rate (eGFR)[7]. If initial tests are normal, they need to be monitored for at least 6-12 mo[8-12]. The renal biopsy should be performed in the case of impaired eGFR, persistent proteinuria, nephrotic (*e.g.*, severe proteinuria, low serum albumin levels and oedema) or nephritic (*e.g.*, impaired eGFR, hypertension, haematuria/proteinuria) syndrome.

This review summarizes some important current aspects of IgAVN and most importantly the understanding of its pathogenesis and treatment founded on the results of a multitude of clinical and experimental researches.

IGA NEPHROPATHY AND IGAVN

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in children and adults. Exclusive renal involvement is characterized by a very slow progression, typical of chronic diseases[9]. In contrast, IgAVN is the most common cause of secondary glomerulonephritis in pediatric age; renal involvement tends to have an acute and self-limiting course similar to that of post-infectious glomerulonephritis, but if persistent it can lead to chronic kidney disease and end-stage renal disease approximately 20 years after diagnosis[10,11].

In a retrospective study based on the epidemiological, clinical and laboratory characteristics of IgAV patients, Carucci *et al*[12] investigated the initial risk factors for IgAVN development, suggesting that age at diagnosis and abdominal pain were associated with a higher risk of onset of the kidney disease in pediatric age. However, additional long-term studies are still needed for the retrospective study type[12].

According to a Japanese study conducted by Komatsu *et al*[13], IgAVN has two peaks in incidence (1-19 years and 60-69 years), while IgAN has an isolated peak in incidence during the 4th decade. Compared to IgAN, IgAVN is clinically more severe (especially considering the parameters of proteinuria and hypoalbuminemia), and histologically more aggressive, with a higher percentage of proliferative endocapillary glomerulonephritis and crescentic glomerulonephritis [13].

Despite these differences, several studies have shown that the two diseases share the same pathogenesis, namely a defect in IgA1 glycosylation[14-16]. In addition, glomerular histologic findings can be identical, ranging from focal proliferative lesions with diffuse mesangial IgA deposits to extracapillary proliferative lesions with crescent formation, making it sometimes impossible to distinguish IgAN from IgAVN in the absence of extrarenal signs. For this reason, the two entities have recently been considered to be two different manifestations of the same pathology and in 2012, during the Chapel Hill Consensus Conference on the nomenclature of vasculitis, it was decided to replace the definition "HSP" with that of "IgAV", considering it the systemic form of IgAN[17,18].

In an interesting case series by Kamei *et al*[10], 11% of patients with an initial diagnosis of IgAN subsequently (over a period ranging from 5 mo to 14 years) developed palpable purpura, which allowed the diagnosis to be changed to IgAVN, supporting the hypothesis that IgAN and IgAVN are actually two variants of the same disease. In almost all of these patients, worsening of nephritis was described after the onset of purpura[10]. For this reason, patients diagnosed with IgAN require careful and prolonged follow-up with special attention to the possible appearance of purpura, a sometimes nuanced finding that therefore risks going unnoticed[19].

PATHOGENESIS

IgAVN shares many pathophysiological features with IgAN (Table 1). The aim of this review is to update the pathogenesis of IgAVN by providing more information regarding impaired glycosylation of IgA1, generation of immune complexes and their kidney deposition, and finally concerning complement activation and stimulation of the mesangial cells, which leads to their expansion and cytokine release[20]. Toll-like-receptor (TLR) activation and B cell proliferation, infection triggers, and genetic factors are also involved in the IgAVN pathogenesis[21].

Infection triggers

Helicobacter pylori[22], *Streptococcus pneumoniae* and *Haemophilus Influenzae*[23,24] are the main pathogens associated with the disease. Infections may be involved in the pathogenesis of IgAVN through two mechanisms. The first is due to the presence of N-acetylgalactosamine (GaINAc) on the superficial side of pathogens stimulating the output of cross-reactive IgA and IgG that identify galactose-deficient IgA1 (Gd-IgA1). Alternatively, microbial agents containing antigens similar to structures on the vessel wall generate a cross-reactive autoantibody response[25].

Table 1 Mechanism of immunoglobulin A vasculitis nephritis pathogenesis

No.	Mechanism of IgAVN pathogenesis
1	Infection triggers (*Helicobacter pylori, Streptococcus pneumoniae* and *Haemophilus Influenzae*[22-25]
2	Genetic factors[26-28]
3	Impaired glycosylation of IgA1 (Gd-IgA1)[29-41]
4	Complement activation[42-45]
5	TLR activation and B cell proliferation[46-48]
6	AECAs[49-51]
7	NAPIr[52,53]
8	Elevated plasma levels of IgE, eosinophil activation, higher levels of ECP and renal α-SMA[54-56]

IgAVN: Immunoglobulin A vasculitis nephritis; Gd-IgA1: Galactose-deficient-immunoglobulin A; TLR: Toll-like-receptor; AECAs: Anti-endothelial cell antibodies; NAPIr: Nephritis-associated plasmin receptor; α-SMA: α-smooth muscle; ECP: Eosinophil cationic protein.

Genetic factors

Little is known yet about the role of genetic factors in the IgAVN pathogenesis, although the presence of ethnic and geographical differences in the incidence of IgAV and IgAVN would indicate its involvement[26,27]. Furthermore, several genes involved in cytokine and chemokine production, complement activation, and regulation of endothelium activity have been implicated in IgAV susceptibility[25,28].

Serum levels of Gd-IgA1 are heritable in both IgAN and IgAVN, indicating that the genetic predisposition to develop IgAVN and IgAN is the same[16].

Impaired glycosylation of IgA1

IgAVN and IgAN appear to have identical pathophysiology, with only quantitative differences[29]. High levels of IgA and IgA-containing immune complexes have been observed in both cases. However, this serum abnormality is not a sensitive marker for diagnosis[30]. IgA1, not IgA2, is the main component of IgAN and IgAVN. The IgA1 molecule has a hinge region which contains up to six O-linked glycan chains made up GaINac, typically with β1,3-linked galactose (Gal) attached to it[31,32]. Normally, mono- and di-sialylated Gal-GaINAc disaccharides are present in healthy subjects[33,34]. Elevated levels of Gd-IgA1 have been detected in patients with IgAVN and IgAN, compared with the healthy population and patients with other glomerular diseases[35]. Therefore, Gd-IgA1 now plays a pivotal role in both IgAN and IgAVN pathogenesis[36].

It has been reported that these patients have decreased galactosylation of O-glycans, resulting in reduced β1,3-galactosyltransferase activity in the peripheral B cells of patients. Reduced β1,3-galactosyltransferase activity leads to a lack of terminal β1,3-galactosyl residues in the hinge region of IgA1[15,37].

Gd-IgA1 polimer molecules are known to be anti-glycan IgA1 or IgG, resulting in the formation of circulating immune complexes that are deposited in the renal mesangium and subepithelial and subendothelial space, and which incite glomerular injury. In IgAVN, IgA deposit can be found not just in the kidney, but also in other sides like the skin, and larger immune complexes are found compared to IgAN[15]. Deposition of IgA1-containing immune complexes appears to be mediated by a relationship with mesangial transferrin 1 (CD71) and CD89 receptors, also known as FcαRI, which may occur as a transmembrane receptor in myeloid cells. These receptors on the mesangial surface are more highly expressed than in healthy children.

The monomeric IgA can bind, but without crossbinding with FcαRI, leading to anti-inflammatory reactions[38]. Monovalent FcαRI targeting results in the formation of intracellular structures called "inhibisomes", which obstruct the signaling of nearby activated receptors. This process is referred to as ITAM inhibitory signaling (ITAMi) and results in a downregulation of immune activation. In contrast, IgA immune complexes binding to FcαRI on neutrophils induce activating ITAM signaling, resulting in multiple pro-inflammatory functions. In addition, the activation of FcαRI induces the LTB4 chemoattractant release, resulting in neutrophil migration[39,40].

Consequently, after deposition the mesangial cells start to proliferate and produce other components of the extracellular matrix, and also inflammatory and profibrogenic cells such as cytokines and chemokines[35-41].

Complement activation

The activation of the complement system plays an important role in the pathophysiology of IgAV and IgAVN, including infection triggers and genetics. Indeed, mesangial deposits contain the complement components C3 and C5-C9, which are able to form the attack complex that destroys the membrane of target cells[42]. High levels of C3a, C5a and Bb have also been documented in the serum of pediatric patients with acute IgAV. C5a is a neutrophil chemoattractant that increases during systemic inflammation. C3a and C5a increase interleukin (IL)-8 secretion by endothelial cells, further attracting neutrophils.

More recently, the lectin-related complement activation pathway has also been shown to be involved in IgAVN and IgAN, as IgA can activate mannan-related lectins[43,44]. In contrast, IgA cannot activate the classic pathway and the main activator of the classic pathway, C1q, which is not present in immune complexes[45].

TLR activation and B cell proliferation

Another mechanism considered to be responsible for IgAV injury is the hyperreactivity of B and T cells in response to specific antigenic triggers. TLR signaling is the first line of defense against microbial infection. Hyperactivated TLR signaling causes cellular inflammatory infiltration that generates cytokines and autoantibodies, leading to autoimmune diseases[46,47].

TLRs are expressed in numerous cells, including kidney cells. There is increasing evidence to support the role for TLRs in autoimmune and inflammatory kidney diseases[22].

Donadio *et al*[48] showed children with IgAV that had significantly increased expression of mRNA encoding for TLR4, compared with healthy controls. TLR2 mRNA expression showed a borderline increase, while no difference was found in the expression of mRNA encoding for TLR3 and TLR9. Regulatory T cells (Treg) expressing the transcriptional factor FoxP3 play a potent anti-inflammatory role. Defective expression of FoxP3 mRNA and reduced expression of transforming growth factor-β1 mRNA were also demonstrated, indicating a defective activity of Treg cells in IgAV[48].

However, it is still unclear if TLR expression is also associated with IgAVN development.

The role of anti-endothelial cell antibodies in IgAVN

Anti-endothelial cell antibodies (AECAs) are a heterogeneous group of antibodies directed to human endothelial cell antigens. A role of these antibodies in IgAVN has been hypothesized[49]. According to the hypothesis, tumor necrosis factor-α can increase the binding of IgA1 AECAs to endothelial cells. The latter produce IL-8, leading to neutrophil migration[50].

The interaction between IgA1 AECAs and FcαRI on neutrophils results in the release of LTB4, inducing neutrophil recruitment, reactive oxygen species release, neutrophil extracellular traps accompanied by the cell death (NETosis) and antibody-dependent cellular cytotoxicity. All this leads to vascular injury in the final analysis[51].

Other possible pathogenic mechanisms of IgAVN

Other pathogenetic mechanisms underlying IgAVN need to be further investigated. Masuda *et al*[52] showed that nephritis-associated plasmin receptor, a nephritogenic antigen for acute poststreptococcal glomerulonephritis, might have a pathogenic role in a subgroup of patients with IgAVN[52].

In a study by Davin *et al*[29], elevated plasma levels of IgE were found more commonly in patients with IgAN, but the pathogenetic role of IgE has not yet been clarified. In fact, mast cells are not usually present in the mesangium[24].

Eosinophil activation, higher levels of eosinophil cationic protein (ECP) in serum, and renal α-smooth muscle (α-SMA) expression have also been proposed as playing a role in the pathogenesis of IgAVN[25].

Observations indicate that enhanced renal α-SMA expression could be an early histological marker of IgAN progression. Similarly, increased expression of α-SMA in the tubule-interstitial region, but not in glomeruli, has been associated with bad prognosis[26].

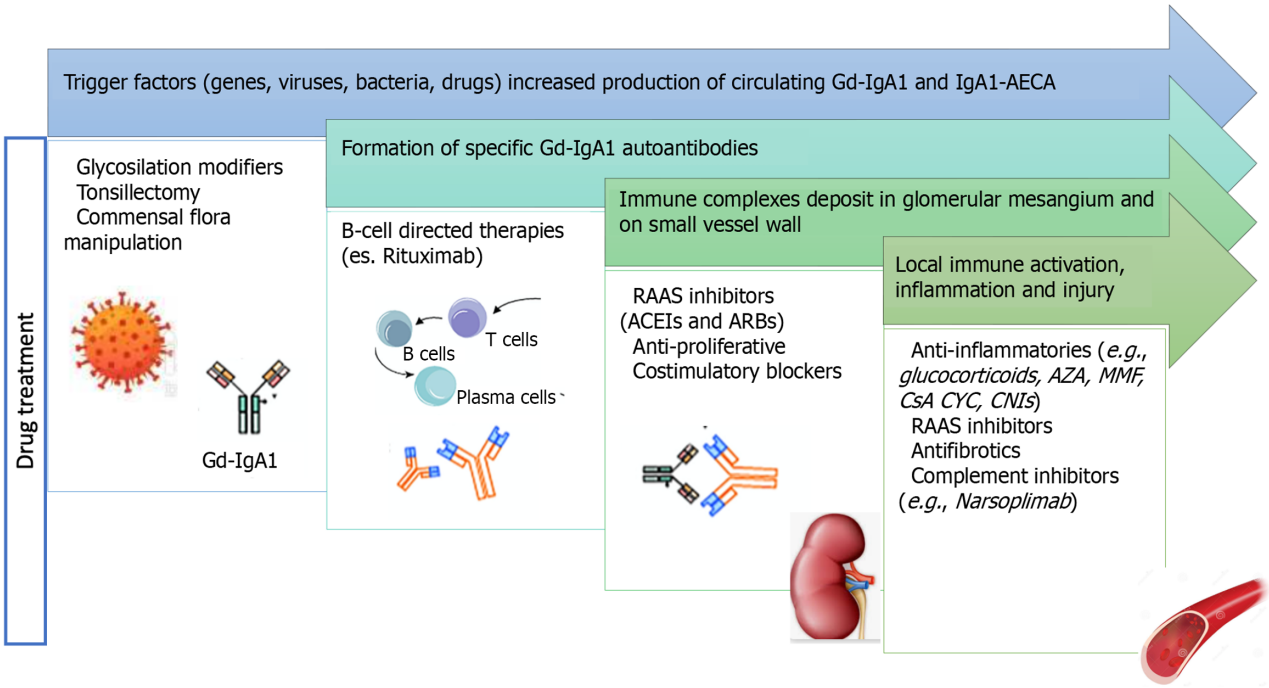
BIOMARKERS

It is currently not possible to predict and identify which children may develop chronic kidney damage from onset. Some serum and urine markers can identify IgAV patients with or without renal involvement and in predicting the severity of renal inflammation to avoid chronic damage[53,54]. Measuring biomarkers in urine has many advantages: Samples are easy to collect using non-invasive methods; urine reflects damages in renal parenchyma, unlike blood, which comes into contact with many organs and organ systems; the number of different core proteins in the urine is lower than in blood [55]. In a prospective, multicenter study, Pillebout *et al*[54] identified biomarkers that may identify IgAVN at the onset of the disease: Serum Gd-IgA1 level, urine IgA, IgG, IgM, IL-6, IL-8, IL-10, and IgA-IgG and IgA-sCD89 complex levels[54]. A systematic literature review performed by Sugino *et al*[56] identifies that some clinical and urinary biomarkers potentially correlate with the presence and severity of IgAVN in children. The most promising preclinical urinary biomarkers in predicting nephritis are: Kidney injury molecule-1 (KIM-1), monocyte chemotactic protein-1 (MCP-1), N-acetyl-β-glucosaminidase (NAG), and angiotensinogen. Urinary KIM-1, MCP-1, and NAG correlate with the disease severity of nephritis (4). However, none of them prove to be established markers of disease. Further studies are needed to verify whether preclinical markers are better than the currently used ones (24-h urinary protein values, urinary protein:creatinine ratio and urinary albumin concentration)[55].

TREATMENT

Figure 1 illustrates the integration of the pathogenesis diagram with the drug treatment diagram to reveal the supporting mechanism of the drugs.

Decisions regarding the treatment of IgAVN are challenging due to the large percentage of patients with a positive prognosis and the uncertain clinical progression of single patients. Unfortunately, evidence-based treatment is not yet



DOI: 10.5527/wjn.v12.i4.82

Figure 1 Pathogenesis and drug treatment for immunoglobulin A vasculitis and nephritis. Gd-IgA1: Galactose-deficient-immunoglobulin A; AECA: Anti-endothelial cell antibodies; RAAS: Renin-angiotensin-aldosterone system; ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; AZA: Azathioprine; MMF: Mycophenolate mofetil; CsA: Cyclosporine A; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors.

available even for the most serious event[1]. In several retrospective studies, delayed therapy has been related to a bad outcome. Therefore, despite the risk of spontaneous remission, it may be recommended that severely affected patients be treated as soon as possible.

Recently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have mainly highlighted that the treatment of IgAVN remains a matter of debate and, in the absence of sufficient long-term data, have recommended that it should be treated in the same way as in patients with non-severe forms of isolated IgAN. However, the KDIGO guidelines do not take into account the more acute onset of IgAVN with more aggressive lesions in renal histology[57]. According to KDIGO guidelines, IgAVN patients should first receive a supporting care including routine modification (smoking cessation, weight control, regular exercise and dietary sodium restriction), blood pressure control and a course of renin-angiotensin system (RAS) blockers without immunosuppressive drugs or steroids. In the opinion of experts, this approach can result in the undertreatment of glomerular inflammation, mainly because acute and potentially aggressive glomerular inflammation goes untouched or its immunosuppressed treatment is postponed for several months.

On the contrary, European treatment guidelines consider IgAN and IgAVN as two distinct entities and suggest oral steroids as a first line therapy in IgAVN. In this regard, the German Society of Pediatric Nephrology has recently suggested an early treatment approach for patients with important kidney involvement. Following this treatment suggestion, IgAVN patients with nephritic syndrome, nephrotic syndrome, or glomerular cellular growths will receive an initial standardized corticosteroid- based treatment regimen for 2 mo, followed by an additional immunosuppression in patients with inadequate response after 3-6 mo from the start of treatment[58].

Corticosteroids, intravenous or oral, are part of most treatment regimens, and there is some evidence of their positive result on the long-term outcome of adult IgAN patients. Similarly, other immunosuppressive therapies, such as azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine A (CsA), or rituximab, have been shown to be effective in individual cases or in small series of patients. Cyclophosphamide (CYC) has also been used for more severe manifestations of IgAN (Table 2)[6]. In conclusion, given the rare nature of severe IgAVN, there is a necessity to standardize the diagnostic and therapeutic approach at least nationally, but ideally multinationally, in order to gain more expertise and move to evidence-based treatment. Future treatment strategies should be evaluated in large multicenter trials. Figure 2 summarizes the treatments available for IgA vasculitis and nephritis.

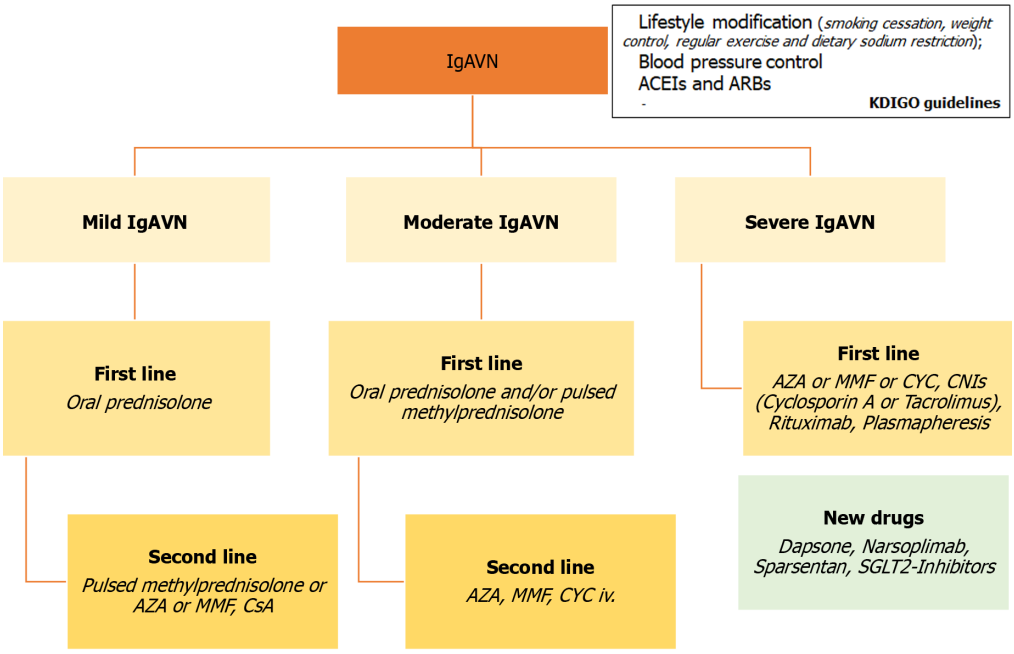
Corticosteroids

Several studies highlight a potential beneficial impact of corticosteroids in IgAVN. Oral prednisolone and/or pulsed methylprednisolone should be used as the earliest treatment in those cases with mild-moderate IgAVN[6]. A randomized, placebo-controlled trial showed that IgAVN was resolved more quickly in children treated with prednisone than in those treated with placebo. However, the study offered outcome data only 6 mo after randomization. Hence, it is unknown whether prednisone treatment reduced the number of cases with persistent IgAVN or simply encouraged a more rapid resolution of the renal disease compared with the placebo[59]. Kim *et al*[60] showed that corticosteroid exposure significantly reduced serum Gd-IgA1 levels, which are associated with the pathophysiology of IgAVN[60].

Table 2 Treatments according to European treatment guidelines

		Class of drugs	Ref.
Mild IgAVN	First line	Corticosteroids: Oral prednisolone	[60-62]
	Second line (or corticosteroid-sparing agent)	Immunosuppressive therapies: Pulsed methylprednisolone or AZA or MMF, CsA	[6,71,72]
Moderate IgAVN	First line	Corticosteroids: Oral prednisolone and/or pulsed methylprednisolone	[6,60-62]
	Second line (Cortico-dependent and cortico-resistant forms of IgAVN)	Immunosuppressive therapies: AZA, MMF, CYC iv	[71,72]
Severe IgAVN	First line	Immunosoppresive therapies + corticosteroids: AZA or MMF or CYC, CNIs (*Cyclosporin A* or *Tacrolimus*), *Rituximab, Plasmapheresis*	[64-66,74-77]
New drugs: *Dapsone, Narsoplimab, Sparsentan*			[81,82]
RAS blockers (*ACEIs* and *ARBs*) should be used in IgAVN as soon as possible			[78-80]

ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; IgAVN: Immunoglobulin A vasculitis nephritis; AZA: Azathioprine; MMF: Mycophenolate mofetil; CsA: Cyclosporine A; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors.



DOI: 10.5527/wjn.v12.i4.82

Figure 2 Therapeutic algoritm for immunoglobulin A vasculitis and nephritis. ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; IgAVN: Immunoglobulin A vasculitis nephritis; AZA: Azathioprine; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors; CsA: Cyclosporine A.

However, no evidence has been found that early treatment with steroids could prevent nephritis in IgAV patients and reduce the risk of proteinuria in the following 12 mo[61].

Other immunosuppressive therapies

In the cortico-dependent and cortico-resistant forms of IgAVN, other immunosuppressive treatments, such as calcineurin inhibitors (CNIs), AZA, MMF, CYC, rituximab and plasmapheresis can be considered. AZA, MMF or intravenous CYC can be used in the first- or second-line management of moderate-severe IgAVN[6].

CNIs should be considered a hopeful agent for the treatment of severe IgAVN. The two CNIs currently on the market are CsA and tacrolimus. CsA was found to be effective in improving histological lesions and proteinuria in IgAVN patients[62,63]. In a pilot study of 20 IgAVN children, 12 of whom received tacrolimus treatment reached complete remission; eight achieved partial remission at the end of 6 mo[64].

Current data are not in favor of CYC use in IgAVN because no statistically significant differences were found in the group of patients treated with this immunosuppressive drug compared to the group treated with high doses of corticosteroid[65,66]. CsA or oral CYC cannot be routinely recommended in moderate IgAVN. Intravenous CYC with pulsed methylprednisolone and/or oral prednisolone are also required as an earliest treatment in patients with IgAVN[6]. AZA

appeared to be an effective steroid-sparing drug. This has allowed all steroid-dependent patients to go steroid-free. No formal guidelines are available for the duration of treatment. In studies no patient has had any adverse events associated with AZA therapy[67,68].

MMF should be suggested patients with IgAVN, especially if proteinuria still remains after an initial steroid course and despite antiproteinuric treatment[69,70]. A current meta-analysis has, in fact, reported results combining eight studies and proposed that patients with IgAN treated with MMF had higher remission than the control group[71]. In association with steroid therapy, AZA and MMF can be used as a maintenance treatment in those patients with severe IgAVN[6].

Data on the use and efficacy of the anti-CD20 monoclonal antibody rituximab in patients with IgAVN are still limited. A few case reports have recommended that rituximab could be successful in IgAVN in both pediatric and adult ages, especially if other oral immunosuppressive treatments have not been able to induce remission[72,73].

Finally, there is plasmapheresis, which can be used as a rescue therapy in cases of rapid progression to renal failure or persistent nephrotic syndrome. Interestingly, early plasmapheresis has been useful in some patients even without additional immunosuppression[74,75].

RAS blockers

Numerous data suggest that RAS blockers such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be used in IgAVN and as soon as possible. Prospective randomized trials have shown that the use of these drugs improves long-term renal issues in children and adults and prevents/Limits secondary glomerular injury in patients with persistent proteinuria[76-78].

New drugs

Dapsone is a drug that could be considered for the treatment of IgAVN because it can suppress the development of toxic-free radicals by neutrophils. It also reduces the output of IgA antibodies, an essential phenomenon in the pathophysiology of IgAVN[79,80].

A phase II study recently demonstrated the safety, tolerability, and efficacy of narsoplimab, a novel Mannan-binding lectin-associated serine proteinase 2 inhibitor. It is a humanized monoclonal antibody that inhibits the lecithin pathway target of the complement system and seems to result in a clinically significant reduction in proteinuria and the stability of renal function as evaluated by eGFR in high-risk patients with IgAN[81].

A clinical trial is being conducted to evaluate the use of sparsentan as a potential first-line treatment in patients with newly diagnosed IgAN who have not received previous treatment with RAS blockers. Treatment response will be based on endpoints of proteinuria and GFR and will be assessed by changes from the baseline compared to another treatment [76].

Many studies have shown the renoprotective role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in early to advanced diabetic kidney disease. Recent evidence show that SGLT2 inhibitors are similarly renoprotective in non-diabetic chronic kidney disease, such as IgAN, in a wide range of eGFR of 25-75 mL/min/1.73 m^2 and albumin/creatinine ratio of 200-5000 mg/g[82,83].

INTERVENTIONS FOR PREVENTING IGAVN

According to a recent Cochran study on the prevention and treatment of IgAVN, studies have shown no benefit of prednisone with respect to placebo or no treatment in preventing persistent kidney disease in children without or with little kidney disease at the time of onset[61].

CONCLUSION

According to the European SHARE initiative, only follow-up is required for patients with microscopic haematuria, no renal disorder and proteinuria, or with non-persistent mild or moderate proteinuria. In the case of severe proteinuria or impaired GFR, a paediatric nephrologist must be consulted and a renal biopsy performed. In the case of mild IgAVN, oral prednisolone should be used as a first-line treatment. In some patients with persistent proteinuria, the addition of AZA or MMF, CsA or pulsed methylprednisolone, may be used as a second-line treatment or as a corticosteroid- sparing agent. For patients with moderate IgAVN, oral prednisolone and/or pulsed methylprednisolone should be used as earliest treatment. Addition of AZA, MMF or intravenous CYC may also be used in the first- or second-line treatment of moderate nephritis, according to the histological findings in the kidney biopsy. For severe IgAVN, intravenous CYC with pulsed methylprednisolone and oral prednisolone should be used as a first-line treatment. AZA/MMF plus steroid therapy can be used as a second life[6].

FOOTNOTES

Author contributions: Amatruda M wrote the article and reviewed the references; Carucci NS wrote the article and revised the references; Chimenz R corrected the article; Conti G thought up the article, supervised the chapters of the article and corrected it.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Italy

ORCID number: Michela Amatruda 0000-0001-9232-777X; Roberto Chimenz 0000-0001-9143-4637; Giovanni Conti 0000-0002-0617-500X.

S-Editor: Fan JR
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Delbet JD**, Parmentier C, Herbez Rea C, Mouche A, Ulinski T. Management of IgA Vasculitis with Nephritis. *Paediatr Drugs* 2021; **23**: 425-435 [PMID: 34396492 DOI: 10.1007/s40272-021-00464-0]
2 **Hastings MC**, Rizk DV, Kiryluk K, Nelson R, Zahr RS, Novak J, Wyatt RJ. IgA vasculitis with nephritis: update of pathogenesis with clinical implications. *Pediatr Nephrol* 2022; **37**: 719-733 [PMID: 33818625 DOI: 10.1007/s00467-021-04950-y]
3 **Kliegman RM**, Stanton B, St. Geme J, Schor NF, Behrman RE. Pediatria di Nelson (19° edizione). *Elsevier* 2013; **910-914**: 1873-1874
4 **Chen JY**, Mao JH. Henoch-Schönlein purpura nephritis in children: incidence, pathogenesis and management. *World J Pediatr* 2015; **11**: 29-34 [PMID: 25557596 DOI: 10.1007/s12519-014-0534-5]
5 **Pohl M**. Henoch-Schönlein purpura nephritis. *Pediatr Nephrol* 2015; **30**: 245-252 [PMID: 24733586 DOI: 10.1007/s00467-014-2815-6]
6 **Ozen S**, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T, Bader-Meunier B, Dolezalova P, Feldman BM, Kone-Paut I, Lahdenne P, McCann L, Pilkington C, Ravelli A, van Royen A, Uziel Y, Vastert B, Wulffraat N, Kamphuis S, Beresford MW. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. *Rheumatology (Oxford)* 2019; **58**: 1607-1616 [PMID: 30879080 DOI: 10.1093/rheumatology/kez041]
7 **Salvador CL**, Tøndel C, Rowe AD, Bjerre A, Brun A, Brackman D, Mørkrid L. Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. *Pediatr Nephrol* 2019; **34**: 301-311 [PMID: 30171354 DOI: 10.1007/s00467-018-4067-3]
8 **Goldstein AR**, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schönlein nephritis. *Lancet* 1992; **339**: 280-282 [PMID: 1346291 DOI: 10.1016/0140-6736(92)91341-5]
9 **Rajasekaran A**, Julian BA, Rizk DV. IgA Nephropathy: An Interesting Autoimmune Kidney Disease. *Am J Med Sci* 2021; **361**: 176-194 [PMID: 33309134 DOI: 10.1016/j.amjms.2020.10.003]
10 **Kamei K**, Ogura M, Sato M, Ito S, Ishikura K. Evolution of IgA nephropathy into anaphylactoid purpura in six cases--further evidence that IgA nephropathy and Henoch-Schonlein purpura nephritis share common pathogenesis. *Pediatr Nephrol* 2016; **31**: 779-785 [PMID: 26679340 DOI: 10.1007/s00467-015-3290-4]
11 **Mao S**, Xuan X, Sha Y, Zhao S, Zhu C, Zhang A, Huang S. Clinico-pathological association of Henoch-Schoenlein purpura nephritis and IgA nephropathy in children. *Int J Clin Exp Pathol* 2015; **8**: 2334-2342 [PMID: 26045740]
12 **Carucci NS**, La Barbera G, Peruzzi L, La Mazza A, Silipigni L, Alibrandi A, Santoro D, Chimenz R, Conti G. Time of Onset and Risk Factors of Renal Involvement in Children with Henoch-Schönlein Purpura: Retrospective Study. *Children (Basel)* 2022; **9** [PMID: 36138703 DOI: 10.3390/children9091394]
13 **Komatsu H**, Fujimoto S, Yoshikawa N, Kitamura H, Sugiyama H, Yokoyama H. Clinical manifestations of Henoch-Schönlein purpura nephritis and IgA nephropathy: comparative analysis of data from the Japan Renal Biopsy Registry (J-RBR). *Clin Exp Nephrol* 2016; **20**: 552-560 [PMID: 26456327 DOI: 10.1007/s10157-015-1177-0]
14 **Çakıcı EK**, Gür G, Yazılıtaş F, Eroğlu FK, Güngör T, Arda N, Orhan D, Özalp Ateş FS, Bülbül M. A retrospective analysis of children with Henoch-Schonlein purpura and re-evaluation of renal pathologies using Oxford classification. *Clin Exp Nephrol* 2019; **23**: 939-947 [PMID: 30895528 DOI: 10.1007/s10157-019-01726-5]
15 **Novak J**, Moldoveanu Z, Renfrow MB, Yanagihara T, Suzuki H, Raska M, Hall S, Brown R, Huang WQ, Goepfert A, Kilian M, Poulsen K, Tomana M, Wyatt RJ, Julian BA, Mestecky J. IgA nephropathy and Henoch-Schoenlein purpura nephritis: aberrant glycosylation of IgA1, formation of IgA1-containing immune complexes, and activation of mesangial cells. *Contrib Nephrol* 2007; **157**: 134-138 [PMID: 17495451 DOI: 10.1159/000102455]
16 **Kiryluk K**, Moldoveanu Z, Sanders JT, Eison TM, Suzuki H, Julian BA, Novak J, Gharavi AG, Wyatt RJ. Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch-Schönlein purpura nephritis. *Kidney Int* 2011; **80**: 79-87 [PMID: 21326171 DOI: 10.1038/ki.2011.16]
17 **Jennette JC**, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**: 1-11 [PMID: 23045170 DOI: 10.1002/art.37715]
18 **Mittal A**, Dijoo M, Sabhikhi A, Gulati S. Henoch Schönlein Purpura Nephritis Developing in a Child with Known IgA Nephropathy. *Indian J Pediatr* 2018; **85**: 808-809 [PMID: 29623535 DOI: 10.1007/s12098-018-2660-x]
19 **Yamabe H**, Kaizuka M, Tsunoda S, Nagasawa T, Nomura K, Shimada M. Henoch-Schönlein Nephritis Manifesting with Purpura 15 years after Diagnosis of IgA Nephropathy. *Case Rep Nephrol* 2019; **2019**: 1042648 [PMID: 31772794 DOI: 10.1155/2019/1042648]
20 **Suzuki H**, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, Wyatt RJ, Scolari F, Mestecky J, Gharavi AG, Julian BA. The

pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; **22**: 1795-1803 [PMID: 21949093 DOI: 10.1681/ASN.2011050464]
21 **Lau KK**, Suzuki H, Novak J, Wyatt RJ. Pathogenesis of Henoch-Schönlein purpura nephritis. *Pediatr Nephrol* 2010; **25**: 19-26 [PMID: 19526254 DOI: 10.1007/s00467-009-1230-x]
22 **Xiong LJ**, Tong Y, Wang ZL, Mao M. Is Helicobacter pylori infection associated with Henoch-Schonlein purpura in Chinese children? a meta-analysis. *World J Pediatr* 2012; **8**: 301-308 [PMID: 23151856 DOI: 10.1007/s12519-012-0373-1]
23 **Senior BW**, Woof JM. The influences of hinge length and composition on the susceptibility of human IgA to cleavage by diverse bacterial IgA1 proteases. *J Immunol* 2005; **174**: 7792-7799 [PMID: 15944283 DOI: 10.4049/jimmunol.174.12.7792]
24 **Wang L**, Li X, Shen H, Mao N, Wang H, Cui L, Cheng Y, Fan J. Bacterial IgA protease-mediated degradation of agIgA1 and agIgA1 immune complexes as a potential therapy for IgA Nephropathy. *Sci Rep* 2016; **6**: 30964 [PMID: 27485391 DOI: 10.1038/srep30964]
25 **Rigante D**, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch-Schönlein purpura? *Autoimmun Rev* 2013; **12**: 1016-1021 [PMID: 23684700 DOI: 10.1016/j.autrev.2013.04.003]
26 **Galla JH**, Kohaut EC, Alexander R, Mestecky J. Racial difference in the prevalence of IgA-associated nephropathies. *Lancet* 1984; **2**: 522 [PMID: 6147580 DOI: 10.1016/s0140-6736(84)92599-6]
27 **Gardner-Medwin JM**, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; **360**: 1197-1202 [PMID: 12401245 DOI: 10.1016/S0140-6736(02)11279-7]
28 **Yu HH**, Liu PH, Yang YH, Lee JH, Wang LC, Chen WJ, Chiang BL. Chemokine MCP1/CCL2 and RANTES/CCL5 gene polymorphisms influence Henoch-Schönlein purpura susceptibility and severity. *J Formos Med Assoc* 2015; **114**: 347-352 [PMID: 25839768 DOI: 10.1016/j.jfma.2012.12.007]
29 **Davin JC**, Ten Berge IJ, Weening JJ. What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? *Kidney Int* 2001; **59**: 823-834 [PMID: 11231337 DOI: 10.1046/j.1523-1755.2001.059003823.x]
30 **de Almeida JL**, Campos LM, Paim LB, Leone C, Koch VH, Silva CA. Renal involvement in Henoch-Schönlein purpura: a multivariate analysis of initial prognostic factors. *J Pediatr (Rio J)* 2007; **83**: 259-266 [PMID: 17551657 DOI: 10.2223/JPED.1638]
31 **Renfrow MB**, Mackay CL, Chalmers MJ, Julian BA, Mestecky J, Kilian M, Poulsen K, Emmett MR, Marshall AG, Novak J. Analysis of O-glycan heterogeneity in IgA1 myeloma proteins by Fourier transform ion cyclotron resonance mass spectrometry: implications for IgA nephropathy. *Anal Bioanal Chem* 2007; **389**: 1397-1407 [PMID: 17712550 DOI: 10.1007/s00216-007-1500-z]
32 **Tarelli E**, Smith AC, Hendry BM, Challacombe SJ, Pouria S. Human serum IgA1 is substituted with up to six O-glycans as shown by matrix assisted laser desorption ionisation time-of-flight mass spectrometry. *Carbohydr Res* 2004; **339**: 2329-2335 [PMID: 15337464 DOI: 10.1016/j.carres.2004.07.011]
33 **Field MC**, Dwek RA, Edge CJ, Rademacher TW. O-linked oligosaccharides from human serum immunoglobulin A1. *Biochem Soc Trans* 1989; **17**: 1034-1035 [PMID: 2628063 DOI: 10.1042/bst0171034]
34 **Baenziger J**, Kornfeld S. Structure of the carbohydrate units of IgA1 immunoglobulin. II. Structure of the O-glycosidically linked oligosaccharide units. *J Biol Chem* 1974; **249**: 7270-7281 [PMID: 4373463]
35 **Amore A**, Cirina P, Conti G, Brusa P, Peruzzi L, Coppo R. Glycosylation of circulating IgA in patients with IgA nephropathy modulates proliferation and apoptosis of mesangial cells. *J Am Soc Nephrol* 2001; **12**: 1862-1871 [PMID: 11518779 DOI: 10.1681/ASN.V1291862]
36 **Lau KK**, Wyatt RJ, Moldoveanu Z, Tomana M, Julian BA, Hogg RJ, Lee JY, Huang WQ, Mestecky J, Novak J. Serum levels of galactose-deficient IgA in children with IgA nephropathy and Henoch-Schönlein purpura. *Pediatr Nephrol* 2007; **22**: 2067-2072 [PMID: 17943324 DOI: 10.1007/s00467-007-0623-y]
37 **Allen AC**, Willis FR, Beattie TJ, Feehally J. Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. *Nephrol Dial Transplant* 1998; **13**: 930-934 [PMID: 9568852 DOI: 10.1093/ndt/13.4.930]
38 **Berthelot L**, Papista C, Maciel TT, Biarnes-Pelicot M, Tissandie E, Wang PH, Tamouza H, Jamin A, Bex-Coudrat J, Gestin A, Boumediene A, Arcos-Fajardo M, England P, Pillebout E, Walker F, Daugas E, Vrtosvnik F, Flamant M, Benhamou M, Cogné M, Moura IC, Monteiro RC. Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J Exp Med* 2012; **209**: 793-806 [PMID: 22451718 DOI: 10.1084/jem.20112005]
39 **Moura IC**, Centelles MN, Arcos-Fajardo M, Malheiros DM, Collawn JF, Cooper MD, Monteiro RC. Identification of the transferrin receptor as a novel immunoglobulin (Ig)A1 receptor and its enhanced expression on mesangial cells in IgA nephropathy. *J Exp Med* 2001; **194**: 417-425 [PMID: 11514599 DOI: 10.1084/jem.194.4.417]
40 **Heineke MH**, Ballering AV, Jamin A, Ben Mkaddem S, Monteiro RC, Van Egmond M. New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura). *Autoimmun Rev* 2017; **16**: 1246-1253 [PMID: 29037908 DOI: 10.1016/j.autrev.2017.10.009]
41 **Moura IC**, Benhamou M, Launay P, Vrtovsnik F, Blank U, Monteiro RC. The glomerular response to IgA deposition in IgA nephropathy. *Semin Nephrol* 2008; **28**: 88-95 [PMID: 18222350 DOI: 10.1016/j.semnephrol.2007.10.010]
42 **Yang YH**, Tsai IJ, Chang CJ, Chuang YH, Hsu HY, Chiang BL. The interaction between circulating complement proteins and cutaneous microvascular endothelial cells in the development of childhood Henoch-Schönlein Purpura. *PLoS One* 2015; **10**: e0120411 [PMID: 25760949 DOI: 10.1371/journal.pone.0120411]
43 **Roos A**, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, Stahl GL, Matsushita M, Fujita T, van Kooten C, Daha MR. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephrol* 2006; **17**: 1724-1734 [PMID: 16687629 DOI: 10.1681/ASN.2005090923]
44 **Hisano S**, Matsushita M, Fujita T, Iwasaki H. Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis. *Am J Kidney Dis* 2005; **45**: 295-302 [PMID: 15685507 DOI: 10.1053/j.ajkd.2004.10.020]
45 **Wyatt RJ**. The complement system in IgA nephropathy and Henoch-Schönlein purpura: functional and genetic aspects. *Contrib Nephrol* 1993; **104**: 82-91 [PMID: 8325036 DOI: 10.1159/000422400]
46 **Gluba A**, Banach M, Hannam S, Mikhailidis DP, Sakowicz A, Rysz J. The role of Toll-like receptors in renal diseases. *Nat Rev Nephrol* 2010; **6**: 224-235 [PMID: 20177402 DOI: 10.1038/nrneph.2010.16]
47 **Amura CR**, Renner B, Lyubchenko T, Faubel S, Simonian PL, Thurman JM. Complement activation and toll-like receptor-2 signaling contribute to cytokine production after renal ischemia/reperfusion. *Mol Immunol* 2012; **52**: 249-257 [PMID: 22750071 DOI: 10.1016/j.molimm.2012.05.020]
48 **Donadio ME**, Loiacono E, Peruzzi L, Amore A, Camilla R, Chiale F, Vergano L, Boido A, Conrieri M, Bianciotto M, Bosetti FM, Coppo R. Toll-like receptors, immunoproteasome and regulatory T cells in children with Henoch-Schönlein purpura and primary IgA nephropathy. *Pediatr Nephrol* 2014; **29**: 1545-1551 [PMID: 24687448 DOI: 10.1007/s00467-014-2807-6]

49 **Legendre P**, Régent A, Thiebault M, Mouthon L. Anti-endothelial cell antibodies in vasculitis: A systematic review. *Autoimmun Rev* 2017; **16**: 146-153 [PMID: 27989761 DOI: 10.1016/j.autrev.2016.12.012]

50 **Yang YH**, Huang YH, Lin YL, Wang LC, Chuang YH, Yu HH, Lin YT, Chiang BL. Circulating IgA from acute stage of childhood Henoch-Schönlein purpura can enhance endothelial interleukin (IL)-8 production through MEK/ERK signalling pathway. *Clin Exp Immunol* 2006; **144**: 247-253 [PMID: 16634798 DOI: 10.1111/j.1365-2249.2006.03076.x]

51 **Otten MA**, Bakema JE, Tuk CW, Glennie MJ, Tutt AL, Beelen RH, van de Winkel JG, van Egmond M. Enhanced FcαRI-mediated neutrophil migration towards tumour colonies in the presence of endothelial cells. *Eur J Immunol* 2012; **42**: 1815-1821 [PMID: 22535639 DOI: 10.1002/eji.201141982]

52 **Masuda M**, Nakanishi K, Yoshizawa N, Iijima K, Yoshikawa N. Group A streptococcal antigen in the glomeruli of children with Henoch-Schönlein nephritis. *Am J Kidney Dis* 2003; **41**: 366-370 [PMID: 12552498 DOI: 10.1053/ajkd.2003.50045]

53 **Williams CEC**, Toner A, Wright RD, Oni L. A systematic review of urine biomarkers in children with IgA vasculitis nephritis. *Pediatr Nephrol* 2021; **36**: 3033-3044 [PMID: 33993342 DOI: 10.1007/s00467-021-05107-7]

54 **Pillebout E**, Jamin A, Ayari H, Housset P, Pierre M, Sauvaget V, Viglietti D, Deschenes G, Monteiro RC, Berthelot L; HSPrognosis group. Biomarkers of IgA vasculitis nephritis in children. *PLoS One* 2017; **12**: e0188718 [PMID: 29190714 DOI: 10.1371/journal.pone.0188718]

55 **Jelusic M**, Sestan M, Giani T, Cimaz R. New Insights and Challenges Associated With IgA Vasculitis and IgA Vasculitis With Nephritis-Is It Time to Change the Paradigm of the Most Common Systemic Vasculitis in Childhood? *Front Pediatr* 2022; **10**: 853724 [PMID: 35372148 DOI: 10.3389/fped.2022.853724]

56 **Sugino H**, Sawada Y, Nakamura M. IgA Vasculitis: Etiology, Treatment, Biomarkers and Epigenetic Changes. *Int J Mol Sci* 2021; **22** [PMID: 34299162 DOI: 10.3390/ijms22147538]

57 **Rovin BH**, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, Cook HT, Fervenza FC, Gibson KL, Glassock RJ, Jayne DRW, Jha V, Liew A, Liu ZH, Mejía-Vilet JM, Nester CM, Radhakrishnan J, Rave EM, Reich HN, Ronco P, Sanders JF, Sethi S, Suzuki Y, Tang SCW, Tesar V, Vivarelli M, Wetzels JFM, Lytvyn L, Craig JC, Tunnicliffe DJ, Howell M, Tonelli MA, Cheung M, Earley A, Floege J. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021; **100**: 753-779 [PMID: 34556300 DOI: 10.1016/j.kint.2021.05.015]

58 **Butzer S**, Hennies I, Gimpel C, Gellermann J, Schalk G, König S, Büscher AK, Lemke A, Pohl M. Early clinical course of biopsy-proven IgA vasculitis nephritis. *BMC Pediatr* 2022; **22**: 570 [PMID: 36195856 DOI: 10.1186/s12887-022-03611-9]

59 **Ronkainen J**, Koskimies O, Ala-Houhala M, Antikainen M, Merenmies J, Rajantie J, Ormälä T, Turtinen J, Nuutinen M. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2006; **149**: 241-247 [PMID: 16887443 DOI: 10.1016/j.jpeds.2006.03.024]

60 **Kim MJ**, Schaub S, Molyneux K, Koller MT, Stampf S, Barratt J. Effect of Immunosuppressive Drugs on the Changes of Serum Galactose-Deficient IgA1 in Patients with IgA Nephropathy. *PLoS One* 2016; **11**: e0166830 [PMID: 27930655 DOI: 10.1371/journal.pone.0166830]

61 **Hahn D**, Hodson EM, Willis NS, Craig JC. Interventions for preventing and treating kidney disease in Henoch-Schönlein Purpura (HSP). *Cochrane Database Syst Rev* 2015; **2015**: CD005128 [PMID: 26258874 DOI: 10.1002/14651858.CD005128.pub3]

62 **Jauhola O**, Ronkainen J, Autio-Harmainen H, Koskimies O, Ala-Houhala M, Arikoski P, Hölttä T, Jahnukainen T, Rajantie J, Ormälä T, Nuutinen M. Cyclosporine A vs. methylprednisolone for Henoch-Schönlein nephritis: a randomized trial. *Pediatr Nephrol* 2011; **26**: 2159-2166 [PMID: 21626222 DOI: 10.1007/s00467-011-1919-5]

63 **Shin JI**, Park JM, Shin YH, Kim JH, Lee JS, Jeong HJ. Henoch-Schönlein purpura nephritis with nephrotic-range proteinuria: histological regression possibly associated with cyclosporin A and steroid treatment. *Scand J Rheumatol* 2005; **34**: 392-395 [PMID: 16234188 DOI: 10.1080/03009740510026544]

64 **Zhang DF**, Hao GX, Li CZ, Yang YJ, Liu FJ, Liu L, Yuan XY, Li RH, Dong L, Dong Q, Jacqz-Aigrain E, Zhao W. Off-label use of tacrolimus in children with Henoch-Schönlein purpura nephritis: a pilot study. *Arch Dis Child* 2018; **103**: 772-775 [PMID: 29535109 DOI: 10.1136/archdischild-2017-313788]

65 **Pillebout E**, Alberti C, Guillevin L, Ouslimani A, Thervet E; CESAR study group. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura. *Kidney Int* 2010; **78**: 495-502 [PMID: 20505654 DOI: 10.1038/ki.2010.150]

66 **Tarshish P**, Bernstein J, Edelmann CM Jr. Henoch-Schönlein purpura nephritis: course of disease and efficacy of cyclophosphamide. *Pediatr Nephrol* 2004; **19**: 51-56 [PMID: 14634864 DOI: 10.1007/s00467-003-1315-x]

67 **Singh S**, Devidayal, Kumar L, Joshi K, Minz RW, Datta U. Severe Henoch-Schönlein nephritis: resolution with azathioprine and steroids. *Rheumatol Int* 2002; **22**: 133-137 [PMID: 12172950 DOI: 10.1007/s00296-002-0208-9]

68 **Sarcina C**, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, Del Vecchio L, Alberghini E, Buzzi L, Baragetti I, Pozzi C. Changes in Proteinuria and Side Effects of Corticosteroids Alone or in Combination with Azathioprine at Different Stages of IgA Nephropathy. *Clin J Am Soc Nephrol* 2016; **11**: 973-981 [PMID: 27129712 DOI: 10.2215/CJN.02300215]

69 **Ren P**, Han F, Chen L, Xu Y, Wang Y, Chen J. The combination of mycophenolate mofetil with corticosteroids induces remission of Henoch-Schönlein purpura nephritis. *Am J Nephrol* 2012; **36**: 271-277 [PMID: 22965140 DOI: 10.1159/000341914]

70 **Han F**, Chen LL, Ren PP, Le JY, Choong PJ, Wang HJ, Xu Y, Chen JH. Mycophenolate mofetil plus prednisone for inducing remission of Henoch-Schönlein purpura nephritis: a retrospective study. *J Zhejiang Univ Sci B* 2015; **16**: 772-779 [PMID: 26365119 DOI: 10.1631/jzus.B1400335]

71 **Du B**, Jia Y, Zhou W, Min X, Miao L, Cui W. Efficacy and safety of mycophenolate mofetil in patients with IgA nephropathy: an update meta-analysis. *BMC Nephrol* 2017; **18**: 245 [PMID: 28724421 DOI: 10.1186/s12882-017-0647-x]

72 **Fenoglio R**, Naretto C, Basolo B, Quattrocchio G, Ferro M, Mesiano P, Beltrame G, Roccatello D. Rituximab therapy for IgA-vasculitis with nephritis: a case series and review of the literature. *Immunol Res* 2017; **65**: 186-192 [PMID: 27449502 DOI: 10.1007/s12026-016-8827-5]

73 **Maritati F**, Fenoglio R, Pillebout E, Emmi G, Urban ML, Rocco R, Nicastro M, Incerti M, Goldoni M, Trivioli G, Silvestri E, Mohammad AJ, Jayne D, Eriksson P, Segelmark M, Novikov P, Harris H, Roccatello D, Vaglio A. Brief Report: Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein). *Arthritis Rheumatol* 2018; **70**: 109-114 [PMID: 28973844 DOI: 10.1002/art.40339]

74 **Shenoy M**, Ognjanovic MV, Coulthard MG. Treating severe Henoch-Schönlein and IgA nephritis with plasmapheresis alone. *Pediatr Nephrol* 2007; **22**: 1167-1171 [PMID: 17530298 DOI: 10.1007/s00467-007-0498-y]

75 **Augusto JF**, Sayegh J, Delapierre L, Croue A, Tollis F, Cousin M, Subra JF. Addition of plasma exchange to glucocorticosteroids for the treatment of severe Henoch-Schönlein purpura in adults: a case series. *Am J Kidney Dis* 2012; **59**: 663-669 [PMID: 22300649 DOI: 10.1053/j.ajkd.2011.12.015]

76 **Ninchoji T**, Kaito H, Nozu K, Hashimura Y, Kanda K, Kamioka I, Shima Y, Hamahira K, Nakanishi K, Tanaka R, Yoshikawa N, Iijima K, Matsuo M. Treatment strategies for Henoch-Schönlein purpura nephritis by histological and clinical severity. *Pediatr Nephrol* 2011; **26**: 563-569 [PMID: 21203777 DOI: 10.1007/s00467-010-1741-5]

77 **Praga M**, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol* 2003; **14**: 1578-1583 [PMID: 12761258 DOI: 10.1097/01.asn.0000068460.37369.dc]

78 **Coppo R**, Peruzzi L, Amore A, Piccoli A, Cochat P, Stone R, Kirschstein M, Linné T. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol* 2007; **18**: 1880-1888 [PMID: 17513327 DOI: 10.1681/ASN.2006040347]

79 **Lee KH**, Hong SH, Jun J, Jo Y, Jo W, Choi D, Joo J, Jung G, Ahn S, Kronbichler A, Eisenhut M, Shin JI. Treatment of refractory IgA vasculitis with dapsone: a systematic review. *Clin Exp Pediatr* 2020; **63**: 158-163 [PMID: 32024340 DOI: 10.3345/kjp.2019.00514]

80 **Iqbal H**, Evans A. Dapsone therapy for Henoch-Schönlein purpura: a case series. *Arch Dis Child* 2005; **90**: 985-986 [PMID: 16113142 DOI: 10.1136/adc.2004.061598]

81 **Lafayette RA**, Rovin BH, Reich HN, Tumlin JA, Floege J, Barratt J. Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy. *Kidney Int Rep* 2020; **5**: 2032-2041 [PMID: 33163724 DOI: 10.1016/j.ekir.2020.08.003]

82 **Tesař V**. SGLT2 inhibitors in non-diabetic kidney disease. *Adv Clin Exp Med* 2022; **31**: 105-107 [PMID: 35077036 DOI: 10.17219/acem/145734]

83 **Wheeler DC**, Toto RD, Stefánsson BV, Jongs N, Chertow GM, Greene T, Hou FF, McMurray JJV, Pecoits-Filho R, Correa-Rotter R, Rossing P, Sjöström CD, Umanath K, Langkilde AM, Heerspink HJL; DAPA-CKD Trial Committees and Investigators. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int* 2021; **100**: 215-224 [PMID: 33878338 DOI: 10.1016/j.kint.2021.03.033]

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2023 September 25; 12(4): 93-103

DOI: 10.5527/wjn.v12.i4.93

ISSN 2220-6124 (online)

MINIREVIEWS

Transcending boundaries: Unleashing the potential of multi-organ point-of-care ultrasound in acute kidney injury

Aisha Batool, Shahzad Chaudhry, Abhilash Koratala

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aydin S, Turkey; Tahtabasi M, Turkey

Received: June 19, 2023
Peer-review started: June 19, 2023
First decision: July 19, 2023
Revised: July 24, 2023
Accepted: September 11, 2023
Article in press: September 11, 2023
Published online: September 25, 2023

Aisha Batool, Abhilash Koratala, Department of Nephrology, Medical College of Wisconsin, Milwaukee, WI 53226, United States

Shahzad Chaudhry, Department of Family Medicine, Advocate Aurora Healthcare, Milwaukee, WI 53202, United States

Corresponding author: Abhilash Koratala, MD, Associate Professor, Department of Nephrology, Medical College of Wisconsin, 8701 W Watertown Plank Road, Room A 7633, Milwaukee, WI 53226, United States. akoratala@mcw.edu

Abstract

Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid increase in serum creatinine levels or a decrease in urine output or both. In spite of thorough history-taking, physical examination, and laboratory analysis, there are limitations in the diagnostic process and clinical monitoring of AKI. Point-of-care ultrasonography (POCUS), a limited ultrasound study performed by clinicians at the bedside, has emerged as a valuable tool in different clinical settings. In this discussion, we explore the potential of POCUS performed by nephrologists to address specific questions encountered in the diagnosis and management of AKI patients. POCUS not only aids in excluding hydronephrosis but also provides real-time insights into hemodynamics, enabling formulation of individualized treatment plans. Further studies are required to assess the impact of multi-organ POCUS on pragmatic patient outcomes related to AKI, as well as its potential in risk stratification and identification of different levels of AKI severity and pathophysiological signatures.

Key Words: Ultrasound; Point-of-care ultrasonography; Doppler; Venous excess Doppler ultrasound; Congestion; Hemodynamics; Heart failure; Nephrology

Core Tip: Point-of-care ultrasound, not limited to kidney is a valuable addition to nephrologists' toolkit, which enhances diagnostic accuracy and guides therapy when properly integrated with clinical and laboratory parameters.

Citation: Batool A, Chaudhry S, Koratala A. Transcending boundaries: Unleashing the potential of multi-organ point-of-care ultrasound in acute kidney injury. *World J Nephrol* 2023; 12(4): 93-103
URL: https://www.wjgnet.com/2220-6124/full/v12/i4/93.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i4.93

INTRODUCTION

Acute kidney injury (AKI) is characterized by a rapid rise in serum creatinine or decrease in urine output or both. It is a clinical syndrome resulting from a variety of hemodynamic, toxic, and structural insults to the kidney, poses a challenge in terms of diagnosis and clinical monitoring, impacting patient outcomes[1,2]. Despite thorough history-taking, physical examination, and laboratory analysis, there are gaps in the diagnostic process and management of AKI. Point-of-care ultrasonography (POCUS) is a limited bedside ultrasound study performed by clinicians as an adjunct to physical examination intended to answer focused clinical questions. There is a growing body of evidence supporting the effectiveness of POCUS in diverse clinical scenarios[3]. As a result, its integration into medical school curricula is becoming more prevalent, and subspecialties are actively working to keep pace with this advancement. In this review, we explore the potential of nephrologist-performed POCUS in addressing specific diagnostic and management questions in AKI patients. From ruling out hydronephrosis to providing real-time hemodynamic insights, integrating POCUS into patient evaluation allows for a comprehensive assessment and the development of individualized treatment plans.

DEFINITION AND CLASSIFICATION OF AKI

According to the Kidney Disease Improving Global Outcomes clinical practice guideline, AKI is defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or increase to ≥ 1.5 times the baseline value within the past 7 d or urine volume < 0.5 mL/kg/h for a duration of 6 h[4]. AKI can be classified into three main categories based on etiology: Hemodynamic causes, urinary tract obstruction, and intrinsic renal diseases. Hemodynamic causes are associated with impaired renal perfusion, while urinary tract obstruction refers to blockages that prevent normal urine flow. Intrinsic renal diseases involve conditions affecting the kidney's internal structures, such as glomerulonephritis or tubulointerstitial diseases. It is important to highlight that what was previously termed *prerenal* AKI is now referred to as *hemodynamic* AKI. While *prerenal* logically suggests any insult occurring before the kidney, it is often misunderstood in clinical practice and used synonymously with volume depletion-related AKI. This narrow interpretation disregards other important factors, such as congestive nephropathy resulting from volume excess or conditions associated with compromised blood supply or renal vasoconstriction. Therefore, the term *hemodynamic* AKI is more comprehensive and encompasses all conditions that can adversely affect renal perfusion. Furthermore, it is noteworthy that while above classification provides a basic framework, AKI etiology in clinical practice is often more complex, with multiple pathologies coexisting. In certain contexts, it may be more appropriate to use a syndrome-based nomenclature, such as cardiorenal, hepatorenal, hepatocardiorenal, or sepsis-associated AKI, to better describe the underlying conditions[1,5]. To maintain simplicity, we will describe the role of POCUS using broad categories of AKI in this review.

POCUS IN HEMODYNAMIC AKI

Accurate assessment of fluid status, or more specifically, hemodynamic assessment, is crucial in the management of hemodynamic AKI. Unfortunately, conventional physical examination lacks sensitivity in this regard, and the introduction of POCUS has significantly improved bedside evaluation[6,7]. POCUS, when performed and interpreted by a skilled practitioner, provides comprehensive information about the entire hemodynamic circuit, and enables informed decision-making regarding the requirement for volume resuscitation or decongestive therapy. The outdated approach of administering intravenous fluids in a trial-and-error manner when volume status is uncertain is no longer justifiable in the era of POCUS. This holds significant importance, especially considering the growing recognition of the detrimental effects of fluid overload on renal and overall outcomes in conditions such as heart failure and critical illness. For instance, in a recent systematic review and meta-analysis including 31076 critically ill patients, for every liter increase in positive fluid balance, the risk of mortality increased by a factor of 1.19 [95% confidence interval (CI): 1.11-1.28][8]. Although association does not imply causation, it is crucial to approach intravenous fluids as medications and administer them only when there is a clear indication. Notably, a recent clinical trial demonstrated the safety of a restrictive fluid management strategy in patients with septic shock, as compared to standard care (*i.e.*, liberal strategy). Although the outcome did not show superiority in the restrictive group, it is worth mentioning that the liberal group received significantly less fluid compared to previous studies that demonstrated harm, with a median of 3.8 liters[9]. In the context of heart failure, the significance of venous congestion causing renal dysfunction *i.e.*, congestive nephropathy is often overlooked in comparison to the forward flow hypothesis, which implicates inadequate cardiac output. However, multiple studies have indicated that elevated central venous pressure (CVP) is associated with deteriorating renal function, even in the presence of preserved cardiac index[10,11]. Conversely, a decrease in glomerular filtration rate (GFR) is observed in heart failure primarily in cases of extremely low cardiac output. For example, in one study, patients

were categorized into three groups based on their cardiac index (CI): CI > 2.0 L/min/m^2 (group A), CI: 1.5 to 2.0 L/min/-m^2 (group B), and CI < 1.5 L/min/m^2 (group C). While all groups exhibited a decrease in the renal fraction of cardiac output and renal blood flow, a significant reduction in GFR was observed only in group C[12].

Our group has previously introduced a goal-directed POCUS strategy for hemodynamic assessment known as the *pump, pipes,* and *the leaks*[13]. The pump refers to focused cardiac ultrasound, pipes represent ultrasound evaluation of the inferior vena cava (IVC) and venous Doppler, while the leaks involve assessing extravascular lung and abdominal fluid (Figure 1).

The pump

The performance and efficiency of the heart directly impact blood flow, organ perfusion, and function. As such, a comprehensive hemodynamic assessment involves evaluation of various cardiac parameters that determine forward flow as well as backward congestion. A subjective assessment of left ventricular (LV) size and motion can provide a qualitative estimate of ejection fraction (EF). This *eyeballing* method has proven to be reasonably accurate when performed by non-cardiologists with minimal training[14]. Additionally, other parameters such as pericardial effusion, valvular dysfunction, and chamber enlargement can be evaluated. Right ventricular (RV) enlargement and interventricular septal flattening are associated with volume overload and/or pressure overload, resulting in a D-shaped LV appearance in the parasternal short axis cardiac view. RV enlargement is often accompanied by functional tricuspid regurgitation, which further contributes to RV overload and increased right atrial pressure (RAP), which can be estimated by IVC POCUS[15, 16]. Nephrologists trained in Doppler applications can assess stroke volume at the bedside by measuring LV outflow tract velocity time integral (LVOT VTI) providing insight into cardiac index, which can be used to distinguish between hypovolemia and euvolemia and low *vs* high cardiac output states (allows for differentiation between patients who would benefit from intravenous fluids and those who require vasopressors or inotropes). In select patients, LVOT VTI can also be used to determine fluid responsiveness, potentially avoiding excessive fluid administration. Furthermore, ability to perform Doppler POCUS enables the evaluation of LV filling pressures, aiding in the titration of diuretic therapy in outpatient settings. For example, in a study involving 1135 patients with heart failure with reduced EF, the group whose management was guided by assessing LV filling pressures and B-type natriuretic peptide levels exhibited a lower incidence of death [hazard ratio (HR): 0.45, $P < 0.0001$] and death or worsening renal function (HR: 0.49, $P < 0.0001$) compared to the standard care group during a median follow-up period of 37.4 mo[17]. Similarly, RV outflow tract Doppler and trans-tricuspid Doppler measurements offer valuable information on pulmonary artery pressures and may help distinguish between precapillary and postcapillary pulmonary hypertension[18-20]. By combining the measurement of LVOT VTI with these Doppler assessments, we can potentially identify patients with AKI who would benefit from further volume removal *vs* those who may require pulmonary vasodilator therapy. This approach allows for a more targeted and individualized treatment strategy based on the specific hemodynamic profile of each patient.

The pipes

IVC ultrasound: Estimating RAP using IVC size and collapsibility is a standard component of comprehensive echocardiography. In spontaneously breathing patients, the current guidelines recommend the following stratification for RAP. If the maximal anteroposterior diameter of IVC is less than 2.1 cm with more than 50% collapse during a sniff, RAP is estimated to be around 3 mmHg (ranging from 0 to 5 mmHg). If the IVC is larger than 2.1 cm and exhibits less than 50% collapse, RAP is recorded as 15 mmHg (ranging from 10 to 20 mmHg). In cases where the IVC parameters do not align with this classification, an intermediate value of 8 mmHg (ranging from 5 to 10 mmHg) is assigned. However, the correlation between IVC parameters and RAP measured through right heart catheterization is modest at best and may not be applicable to mechanically ventilated patients[21-23]. It is also unreliable in conditions such as intraabdominal hypertension. Moreover, IVC POCUS is susceptible to various technical challenges such as cylinder effect, limiting its practical usefulness, particularly when interpreted in isolation[24]. Nevertheless, the assessment of IVC can still serve as an indicator of fluid tolerance, as an engorged IVC often indicates elevated RAP in patients with a high likelihood of fluid overload. In other words, such patients have increased right-sided filling pressures and may not tolerate intravenous fluid administration.

Alternatives to IVC ultrasound: POCUS of other systemic veins such as the internal jugular vein (IJV) and superior vena cava (SVC) can be utilized for non-invasive estimation of RAP, particularly when the IVC is not accessible or unreliable (*e.g.*, liver disease, abdominal surgery). Most clinicians are familiar with estimating jugular venous pressure through visual inspection of IJV, but it lacks sensitivity; the use of POCUS enables improved identification of the vein. In a recent study, an IJV maximal diameter of ≥ 1.2 cm or respiratory variation in diameter of < 30% showed specificity > 70% for elevated filling pressure (RAP ≥ 10 mmHg). Combining IJV POCUS with physical examination improved the combined specificity to 97% for RAP ≥ 10 mmHg[25]. In another study, less than 17% increase in the cross-sectional area of the right IJV with Valsalva maneuver predicted an elevated RAP (> 12 mmHg) with 90% sensitivity and 74% specificity[26]. In patients with cirrhosis, Leal-Villarreal *et al*[27] found that IJV POCUS predicts RAP better than IVC. Interestingly, satisfactory IVC images were not attainable in 18% of the cases[27]. SVC provides comparable information about RAP since it is another vessel that enters the right atrium like IVC. However, it's not routinely used in point of care settings as transesophageal echocardiography is generally needed to obtain reliable images of the vessel. Nevertheless, Doppler ultrasound of the SVC through the subcostal transthoracic window is emerging as a viable alternative[28].

Venous congestion assessment by Doppler ultrasound: The assessment of Doppler patterns in abdominal veins has been a subject of study for several decades. However, it was not until 2020 that Beaubien-Souligny *et al*[29] introduced the concept of venous excess ultrasound or Venous Excess Doppler UltraSound (VExUS), which has significantly transf-

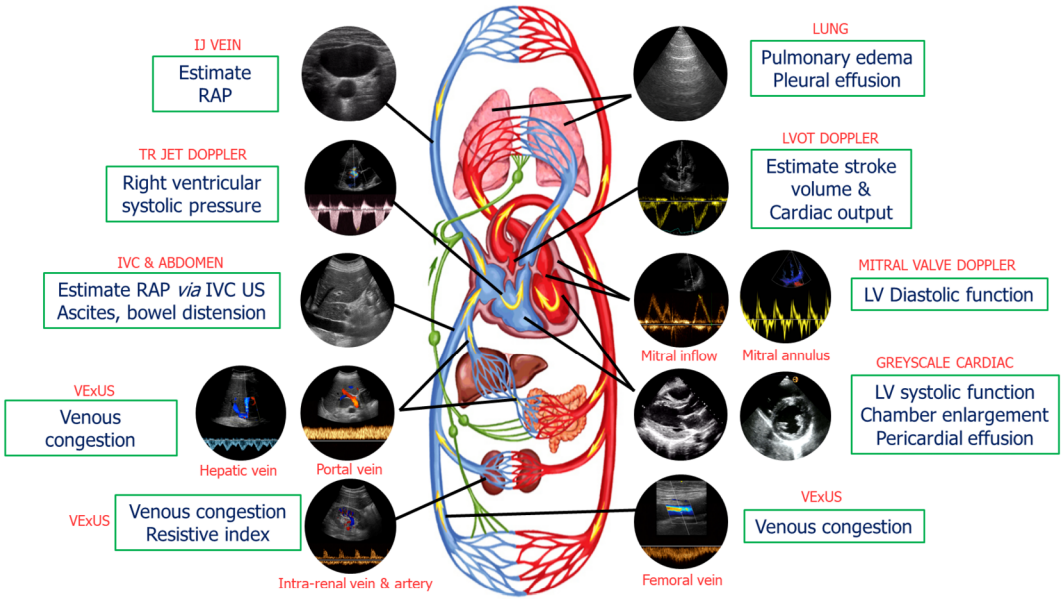


Figure 1 Common sonographic applications used by trained clinicians at the bedside in the evaluation of acute kidney injury. It is important to evaluate multiple points of the hemodynamic circuit instead of relying on isolated parameters. IJ: Internal jugular; RAP: Right atrial pressure; TR: Tricuspid regurgitation; IVC: Inferior vena cava; US: Ultrasound; VExUS: venous excess ultrasound; LV: Left ventricular; LVOT: Left ventricular outflow tract. Citation: Koratala A, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; 3: 1965-1968. Copyright© 2022 by the American Society of Nephrology (corresponding author's prior open access publication).

ormed our noninvasive evaluation of congestion at the bedside. Among their group of patients who underwent cardiac surgery, it was observed that the occurrence of significant flow abnormalities in two or more veins (hepatic, portal, and kidney parenchymal veins) combined with an enlarged IVC (≥ 2 cm) proved to be a more effective predictor of AKI risk (HR: 3.69; 95%CI: 1.65-8.24; P = 0.001) compared to isolated CVP measurements[29]. In other words, direct assessment of venous congestion using Doppler ultrasound offers more comprehensive information regarding congestive organ injury compared to isolated ultrasound of the IVC or IJV. Additionally, since these waveforms are dynamic in nature, VExUS serves as a valuable bedside tool for monitoring the effectiveness of decongestive therapy in real time[30-32]. Figure 2 depicts the transformation of individual Doppler waveforms with increasing RAP as well as the VExUS grading system. It is important to highlight that VExUS is not limited to cardiac surgery or heart failure patients. A recent study by Rihl *et al*[33] demonstrated its applicability in an unselected cohort of patients admitted to the medical intensive care unit. The study found that patients who had reduction in their VExUS score through decongestive therapy had a significantly higher number of days free from renal replacement therapy at Day 28 compared to those who did not achieve a reduction (28 *vs* 15, P = 0.012). Moreover, CVP alone was unable to distinguish between patients with no/mild congestion and those with severe congestion[33]. VExUS is determined by both RAP and venous compliance, making it a comprehensive measure of venous congestion. Merely measuring RAP alone does not necessarily provide information about the extent of venous congestion.

Extended VExUS: The concept of E-VExUS, or extended VExUS, has been introduced to incorporate Doppler evaluation of additional veins like the internal jugular, SVC, splenic, and femoral veins[34]. Figure 3 depicts components of E-VExUS. This extension is particularly useful when the primary veins have certain limitations (such as hepatic and portal veins in cirrhosis or intrarenal veins in advanced kidney disease). Like the components of the original VExUS, these veins have also been studied individually and demonstrated their usefulness in identifying elevated RAP[28,35-38]. Lately, there has been a surge in interest regarding femoral vein Doppler because of its relatively straightforward image acquisition process. In a recent study, the accuracy of both VExUS score and femoral vein Doppler in detecting venous congestion was reported as 80.37 (95%CI: 71.5-87.4) and 74.7 (95%CI: 65.4-82.6), respectively[39]. Nevertheless, the use of E-VExUS is still in the early phases of implementation, and further data are required to determine its clinical utility in routine practice.

Renal arterial resistive index: In principle, the measurement of intra-renal arterial resistive index (RI) is an appealing method to assess renal perfusion, and it has been studied in various clinical scenarios such as heart failure, septic shock, and hepatorenal syndrome, showing some usefulness[40-43]. The RI is calculated using the formula (peak systolic velocity-end diastolic velocity)/peak systolic velocity within a given cardiac cycle (Figure 4A). However, the RI is influenced by multiple renal and non-renal variables including pulse pressure, heart rate, arteriosclerosis, vasoconstriction, venous congestion, underlying chronic kidney disease, valvular diseases like aortic stenosis, as well as medications, which limits its practical utility[44]. RI has also been a subject of interest in the evaluation of renal artery stenosis (RAS), but its diagnostic value remains non-specific. In our clinical practice, we rely on computed tomography (CT) or magnetic resonance angiography to evaluate patients with uncontrolled hypertension and a high suspicion for

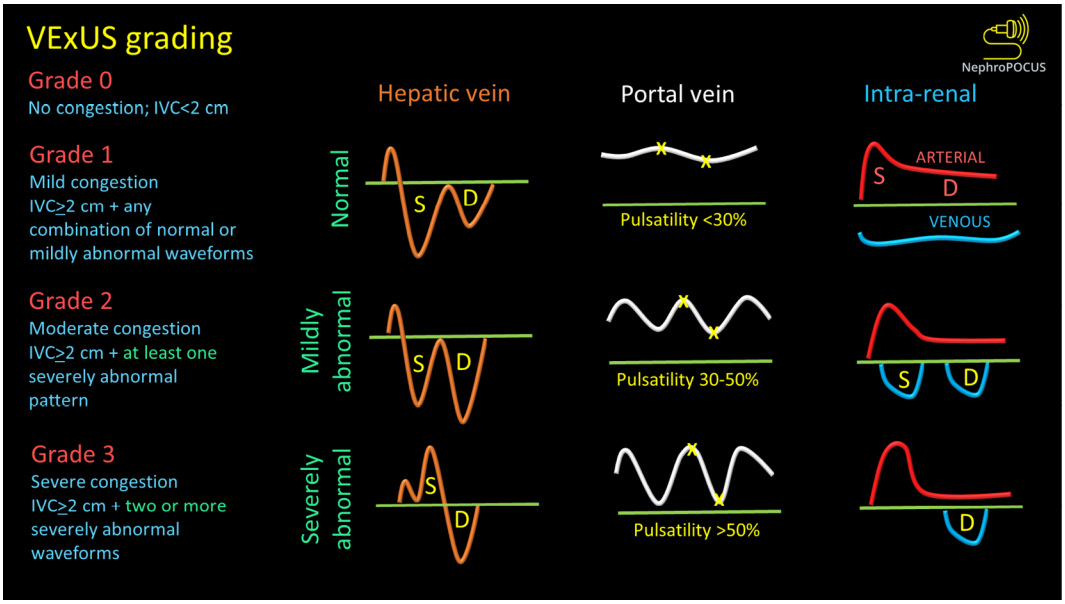


Figure 2 VexUS (Venous Excess Doppler UltraSound) grading system: When the diameter of inferior vena cava is > 2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (D) wave, but still below the baseline; it is considered severely abnormal when the S-wave is reversed. Portal vein Doppler is considered mildly abnormal when the pulsatility is 30% to 50%, and severely abnormal when it is ≥ 50%. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with D-only pattern. Figure adapted from NephroPOCUS.com with permission (corresponding author's educational website)-https://nephropocus.com/2021/10/05/vexus-flash-cards/.

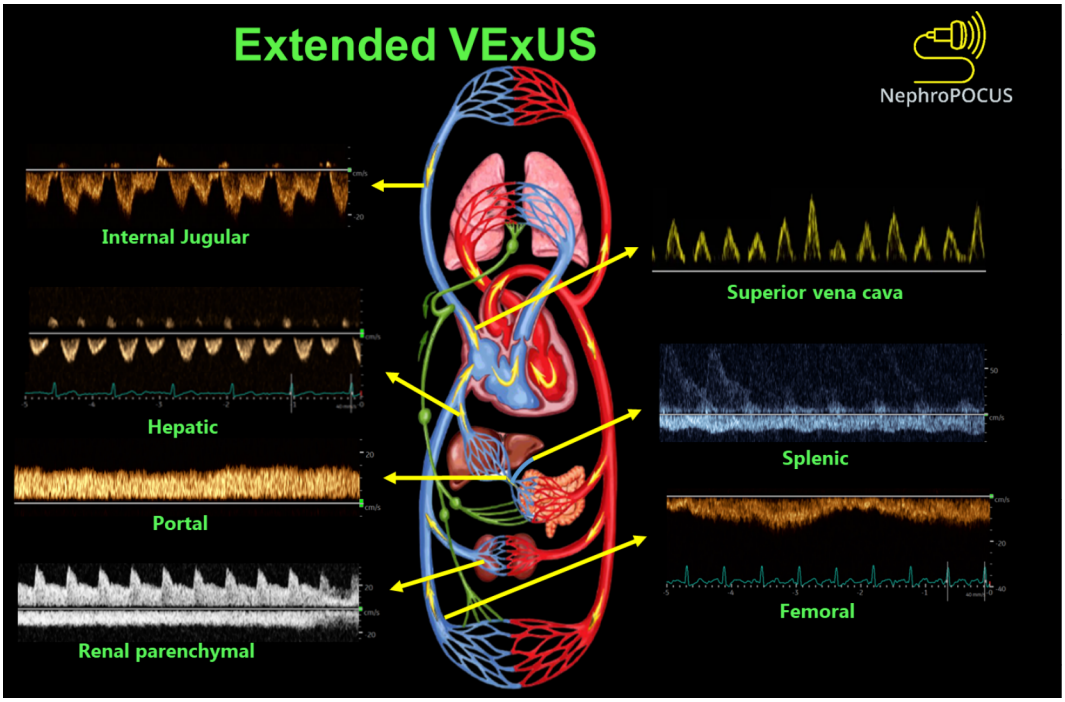
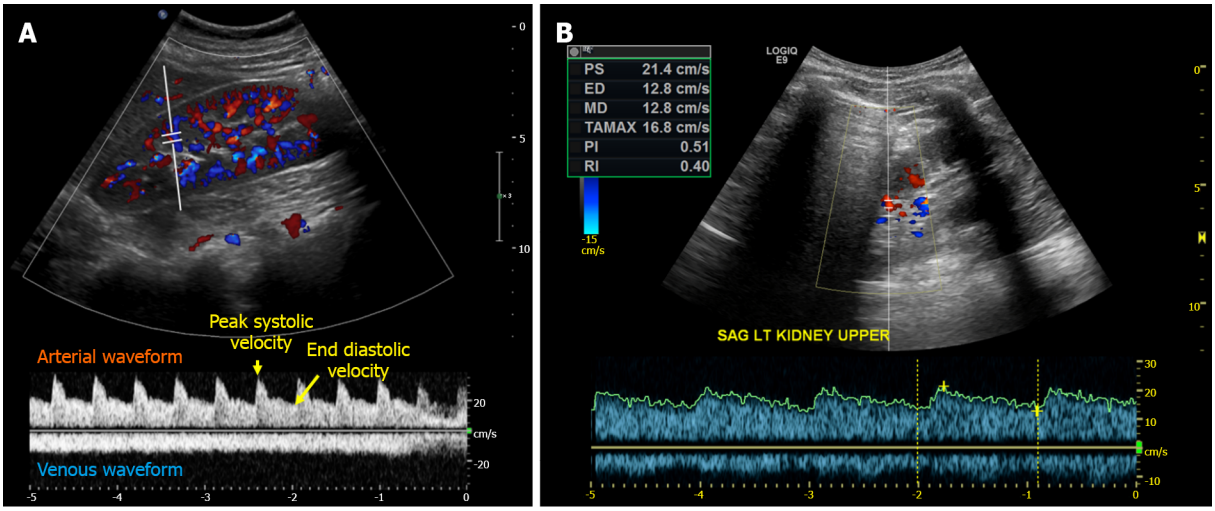


Figure 3 Doppler components of extended VexUS examination. Figure adapted from NephroPOCUS.com with permission (corresponding author's educational website)-https://nephropocus.com/2022/11/28/hemodynamic-pocus-in-cirrhosis-think-beyond-the-ivc/.

RAS instead of POCUS. However, in some cases of RAS, a *Tardus parvus* waveform may be noted by the POCUS-performing physician, which should prompt further investigation. It is characterized by a slow upstroke and rounding of the systolic peak, relatively specific for RAS when found, resulting from proximal stenosis and reduced blood flow (Figure 4B). Additionally, based on our experience, there is significant variability both between different operators and within the same operator when reporting the RI, making it less reliable for monitoring response to therapeutic interventions in the point of care settings. Moreover, intrarenal Doppler in general is technically challenging to perform in



DOI: 10.5527/wjn.v12.i4.93 **Copyright** ©The Author(s) 2023.

Figure 4 Intrarenal Doppler demonstrating normal waveforms, Tardus Parvus waveform in a case of renal artery stenosis. A: Normal waveforms; B: Tardus Parvus waveform.

critically ill patients. On the contrary, intra-renal venous Doppler is a more reproducible and less error-prone method due to its qualitative nature, which involves waveform analysis without the requirement for precise measurements. Moreover, venous congestion may explain the elevated RI observed in patients with volume overload, as it increases the resistance to arterial diastolic flow.

The leaks

POCUS is a sensitive bedside tool to detect extravascular lung water and ascites, both of which have important management implications in the treatment of AKI (*e.g.*, determine the amount of ultrafiltration in patients requiring renal replacement therapy, titrate diuretic dosing, gauge fluid tolerance when contemplating intravenous fluid therapy or assess the need for therapeutic paracentesis). In a systematic review and meta-analysis including a total of 8 studies reporting on 2787 patients, lung POCUS was found to be more sensitive (91.8% *vs* 76.5%) and specific (92.3% *vs* 87.0%) than chest radiography for the detection of cardiogenic pulmonary edema[45]. Similarly, lung POCUS has been shown to detect small pleural effusions with a higher diagnostic accuracy than lateral decubitus chest radiography[46]. With respect to ascites, the superiority of ultrasound to physical examination and radiography has been long recognized[47]. Notably, unlike Doppler ultrasound, both these sonographic applications are much easier to learn with short training.

Figure 5 provides an Overview of common ultrasound findings in nephrology-relevant hemodynamic phenotypes.

POCUS IN INTRINSIC RENAL AKI

The usefulness of POCUS in determining the underlying cause of intrinsic AKI is limited. Parameters such as cortical echogenicity, thickness and renal length can provide some insights when considered in the appropriate clinical context but lack specificity (Figure 6)[48]. For instance, in cases where the baseline serum creatinine is unavailable, a small kidney size and increased cortical echogenicity may suggest a lower likelihood of treatable disease[49]. Conversely, enlarged kidneys with preserved parenchymal thickness and increased cortical echogenicity must prompt further investigation for infiltrative diseases like amyloidosis and malignancy, although these findings alone are not diagnostic. Of note, increased cortical echogenicity is seen in any renal parenchymal disease, regardless of acute or chronic process (*e.g.*, acute tubular necrosis, acute interstitial nephritis, acute glomerulonephritis, and chronic kidney disease)[50].

POCUS IN OBSTRUCTIVE AKI

Clinicians skilled in POCUS can easily identify urinary obstruction through bedside POCUS, leading to prompt diagnosis and timely intervention to relieve the obstruction, thereby preventing a decline in GFR. In one study, internist-performed POCUS demonstrated a sensitivity of 90% and a specificity of 100% for urinary tract obstruction in patients with AKI. Furthermore, the negative predictive value was 99%, indicating that it is a valuable tool that can potentially reduce the need for departmental ultrasound[51]. Similarly, in a study performed in the emergency setting, when compared to the consensus radiology interpretation of POCUS as the reference standard, emergency physicians demonstrated an overall sensitivity of 85.7% (95%CI: 84.3%-87.0%), specificity of 65.9% (95%CI: 63.1%-68.7%), positive likelihood ratio of 2.5 (95%CI: 2.3-2.7), and negative likelihood ratio of 0.22 (95%CI: 0.19-0.24) for detecting hydronephrosis[52]. On a note of

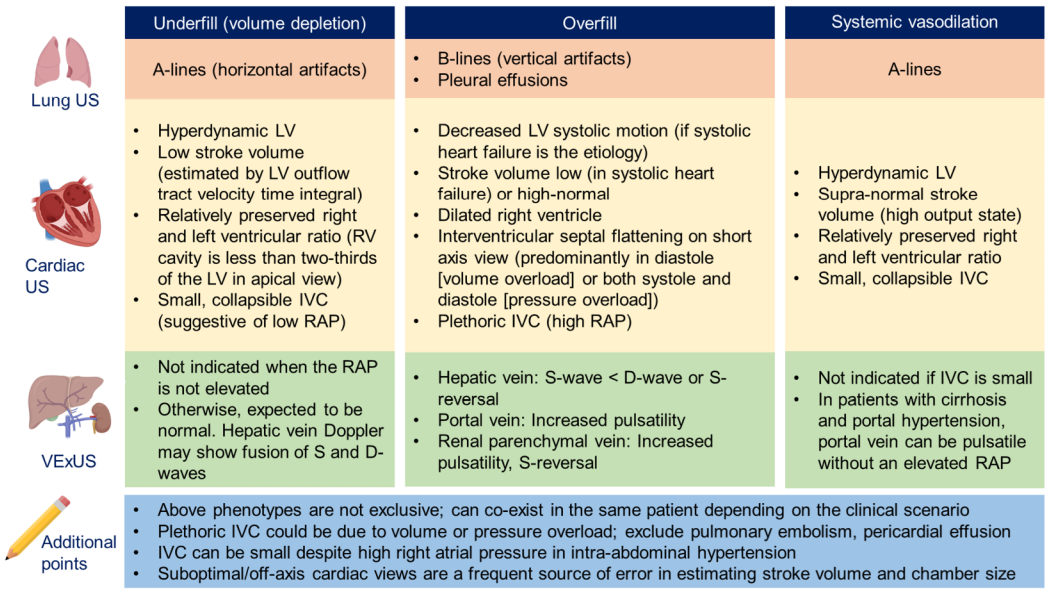


Figure 5 Overview of common ultrasound findings in nephrology-relevant hemodynamic phenotypes. Systemic vasodilation is frequently seen in patients with liver cirrhosis or early sepsis and renal dysfunction. Underfill phenotype primarily denotes volume depletion. IVC: Inferior vena cava; LV: Left ventricle; RAP: Right atrial pressure; US: Ultrasound; VExUS: Venous excess Doppler ultrasound. Citation: Taleb Abdellah A, Koratala A. Nephrologist-Performed Point-of-Care Ultrasound in Acute Kidney Injury: Beyond Hydronephrosis. *Kidney Int Rep* 2022; 7: 1428-1432. Copyright© 2022 International Society of Nephrology. Published by Elsevier Inc. (corresponding author's prior open access publication).

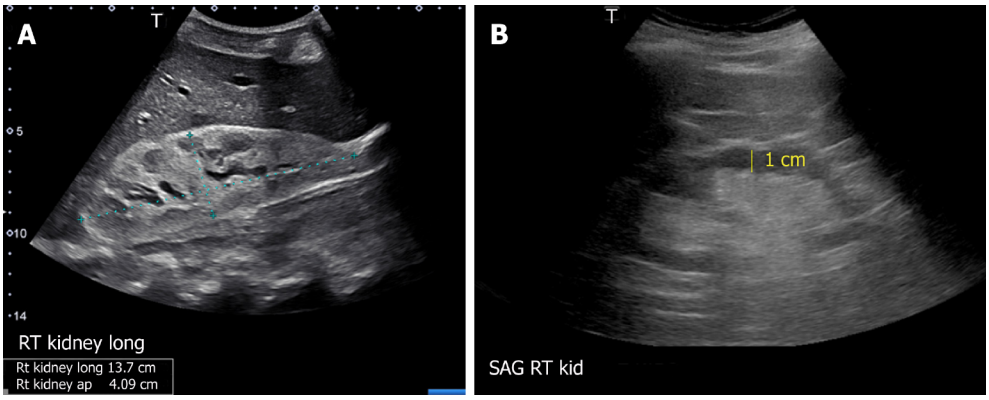


Figure 6 Renal sonogram demonstrating (A) large hyperechogenic kidney in a patient with multiple myeloma and (B) thin parenchyma approximately 1 cm in a patient with chronic kidney disease (normal parenchymal thickness: 1.5-2 cm). Citation: Koratala A, Bhattacharya D, Kazory A. Point of care renal ultrasonography for the busy nephrologist: A pictorial review. *World J Nephrol* 2019; 8: 44-58. Copyright© The Author(s) 2019. Published by Baishideng Publishing Group Inc. (corresponding author's prior open access publication).

caution, novice POCUS users should be aware of common ultrasound findings that can mimic hydronephrosis, including parapelvic cysts, extrarenal pelvis, and vascular malformations[53]. Figure 7 illustrates sonographic appearance of hydronephrosis and its qualitative grading. POCUS also allows timely identification of urinary bladder abnormalities such as urine retention, blocked or misplaced Foley catheter, urinary stones, masses, and prostatomegaly[50].

CONCLUSION

Multi-organ POCUS serves as a valuable complement to physical examination when evaluating AKI. While the use of POCUS by nephrologists has gained attention, several practical challenges exist. Currently, only a small number of nephrology fellowship programs provide comprehensive training in diagnostic POCUS beyond kidney ultrasound[54]. A significant barrier to widespread training is the limited availability of faculty who are proficient in ultrasound and have dedicated time for teaching. It is crucial for professional societies to collaborate in developing standardized guidelines, competency standards, and methods for ongoing training to support POCUS training in nephrology. While current studies mainly focus on initial training, additional research is needed to determine the optimal strategies for longitudinal training to maintain proficiency in POCUS skills. Additionally, while POCUS examinations ideally only take a few extra

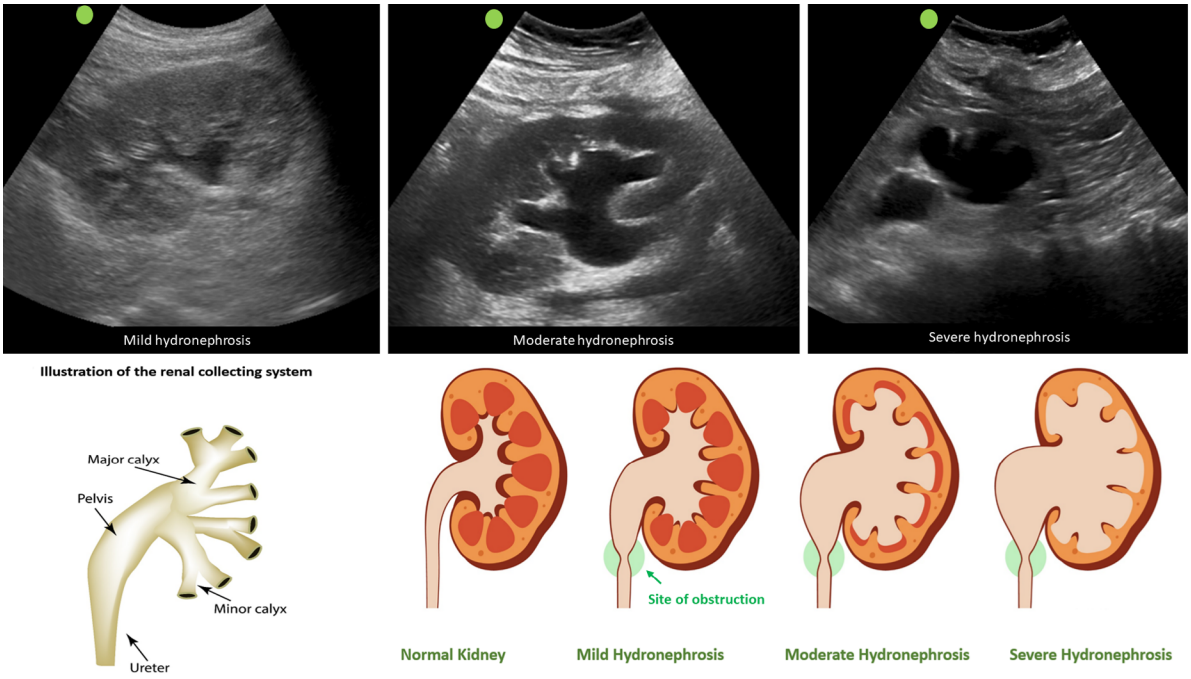


Figure 7 Sonographic appearance of hydronephrosis and its qualitative grading. Hydronephrosis appears as an anechoic (black) branching structure representing dilated collecting system. Citation: Koratala A. The Ultrasound Mimics of Hydronephrosis. Renal Fellow Network. [cited 18 June 2023]. Available from: https://www.renalfellow.org/2019/05/10/the-ultrasound-mimics-of-hydronephrosis/#:~:text=Prominent%20renal%20vasculature%20and%20vascular,also%20appears%20black%20on%20ultrasound. Copyright© 2019. Published by Renal Fellow Network (corresponding author's prior open access publication).

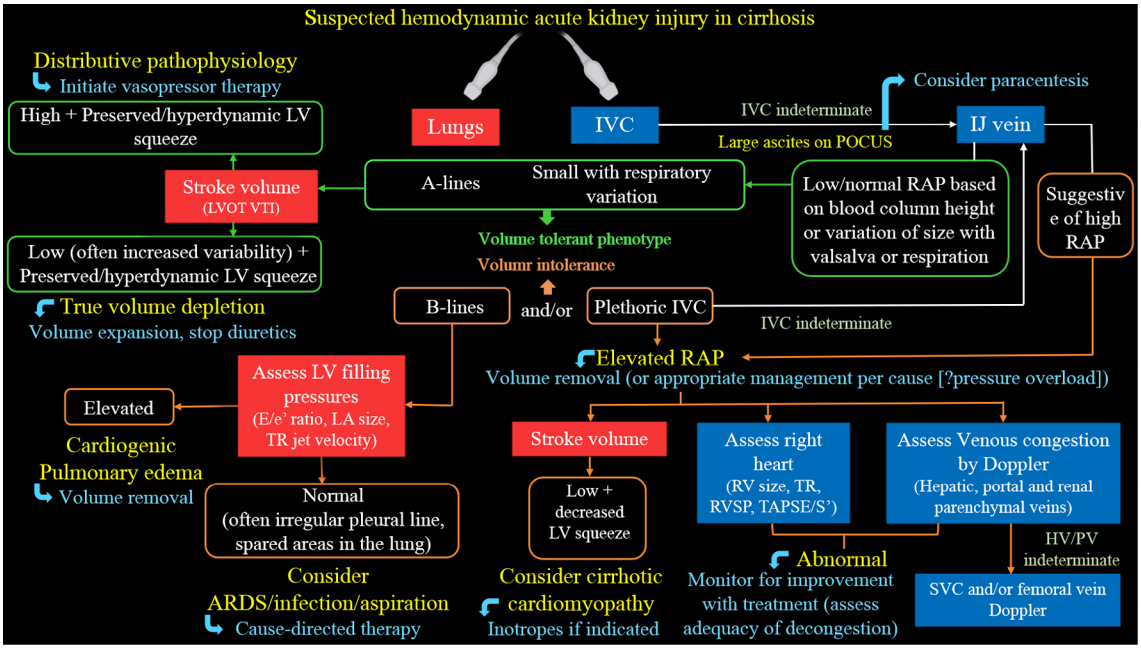


Figure 8 Proposed diagnostic algorithm for approaching acute kidney injury in a patient with cirrhosis. Citation: Koratala A, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; 3: 1965-1968. Copyright© 2022 by the American Society of Nephrology (corresponding author's prior open access publication).

minutes, the cumulative time burden for physicians with heavy patient loads should be considered. Another priority is the development of practical POCUS protocols tailored to specific areas of clinical need, such as the evaluation of hyponatremia, hepatorenal syndrome, and cardiorenal syndrome. For example, Figure 8 presents a sample protocol outlining the evaluation of patients with hepatorenal dysfunction using the aforementioned sonographic applications [55]. This protocol serves as a visual guide, illustrating the step-by-step approach for utilizing POCUS in guiding management of these patients. Finally, it is important to acknowledge that performing POCUS without proper training or overestimating one's skills, as well as the capabilities of the equipment, can potentially lead to misdiagnosis and patient

harm.

FOOTNOTES

Author contributions: Batool A and Chaudhry S drafted the manuscript; Koratala A designed the manuscript, reviewed, and revised for critical intellectual content; All authors have read and approved the final version.

Conflict-of-interest statement: The authors declare no potential conflicts of interest. Abhilash Koratala reports research funding from KidneyCure and the American Society of Nephrology's William and Sandra Bennett Clinical Scholars Grant.

Country/Territory of origin: United States

ORCID number: Abhilash Koratala 0000-0001-5801-3574.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Ronco C**, Bellomo R, Kellum JA. Acute kidney injury. *Lancet* 2019; **394**: 1949-1964 [PMID: 31777389 DOI: 10.1016/S0140-6736(19)32563-2]
2 **Kellum JA**, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. *Nat Rev Dis Primers* 2021; **7**: 52 [PMID: 34267223 DOI: 10.1038/s41572-021-00284-z]
3 **Koratala A**, Kazory A. An Introduction to Point-of-Care Ultrasound: Laennec to Lichtenstein. *Adv Chronic Kidney Dis* 2021; **28**: 193-199 [PMID: 34906303 DOI: 10.1053/j.ackd.2021.07.002]
4 Section 2: AKI Definition. *Kidney Int Suppl (2011)* 2012; **2**: 19-36 [PMID: 25018918 DOI: 10.1038/kisup.2011.32]
5 **Kazory A**, Ronco C. Hepatorenal Syndrome or Hepatocardiorenal Syndrome: Revisiting Basic Concepts in View of Emerging Data. *Cardiorenal Med* 2019; **9**: 1-7 [PMID: 30223273 DOI: 10.1159/000492791]
6 **McGee S**, Abernethy WB 3rd, Simel DL. The rational clinical examination. Is this patient hypovolemic? *JAMA* 1999; **281**: 1022-1029 [PMID: 10086438 DOI: 10.1001/jama.281.11.1022]
7 **Koratala A**, Ronco C, Kazory A. Diagnosis of Fluid Overload: From Conventional to Contemporary Concepts. *Cardiorenal Med* 2022; **12**: 141-154 [PMID: 36096121 DOI: 10.1159/000526902]
8 **Messmer AS**, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid Overload and Mortality in Adult Critical Care Patients-A Systematic Review and Meta-Analysis of Observational Studies. *Crit Care Med* 2020; **48**: 1862-1870 [PMID: 33009098 DOI: 10.1097/CCM.0000000000004617]
9 **Meyhoff TS**, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, Jakob SM, Cecconi M, Nalos M, Ostermann M, Malbrain M, Pettilä V, Møller MH, Kjær MN, Lange T, Overgaard-Steensen C, Brand BA, Winther-Olesen M, White JO, Quist L, Westergaard B, Jonsson AB, Hjortsø CJS, Meier N, Jensen TS, Engstrøm J, Nebrich L, Andersen-Ranberg NC, Jensen JV, Joseph NA, Poulsen LM, Herløv LS, Sølling CG, Pedersen SK, Knudsen KK, Straarup TS, Vang ML, Bundgaard H, Rasmussen BS, Aagaard SR, Hildebrandt T, Russell L, Bestle MH, Schønemann-Lund M, Brøchner AC, Elvander CF, Hoffmann SKL, Rasmussen ML, Martin YK, Friberg FF, Seter H, Aslam TN, Ådnøy S, Seidel P, Strand K, Johnstad B, Joelsson-Alm E, Christensen J, Ahlstedt C, Pfortmueller CA, Siegemund M, Greco M, Raděj J, Kříž M, Gould DW, Rowan KM, Mouncey PR, Perner A; CLASSIC Trial Group. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. *N Engl J Med* 2022; **386**: 2459-2470 [PMID: 35709019 DOI: 10.1056/NEJMoa2202707]
10 **Tabucanon T**, Tang WHW. Right Heart Failure and Cardiorenal Syndrome. *Cardiol Clin* 2020; **38**: 185-202 [PMID: 32284096 DOI: 10.1016/j.ccl.2020.01.004]
11 **Husain-Syed F**, Gröne HJ, Assmus B, Bauer P, Gall H, Seeger W, Ghofrani A, Ronco C, Birk HW. Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives. *ESC Heart Fail* 2021; **8**: 183-203 [PMID: 33258308 DOI: 10.1002/ehf2.13118]
12 **Ljungman S**, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. *Drugs* 1990; **39** Suppl 4: 10-21; discussion 22 [PMID: 2354670 DOI: 10.2165/00003495-199000394-00004]
13 **Koratala A**, Kazory A. Point of Care Ultrasonography for Objective Assessment of Heart Failure: Integration of Cardiac, Vascular, and Extravascular Determinants of Volume Status. *Cardiorenal Med* 2021; **11**: 5-17 [PMID: 33477143 DOI: 10.1159/000510732]
14 **Moore CL**, Rose GA, Tayal VS, Sullivan DM, Arrowood JA, Kline JA. Determination of left ventricular function by emergency physician echocardiography of hypotensive patients. *Acad Emerg Med* 2002; **9**: 186-193 [PMID: 11874773 DOI: 10.1111/j.1553-2712.2002.tb00242.x]
15 **Denault AY**, Langevin S, Lessard MR, Courval JF, Desjardins G. Transthoracic echocardiographic evaluation of the heart and great vessels. *Can J Anaesth* 2018; **65**: 449-472 [PMID: 29352414 DOI: 10.1007/s12630-018-1068-4]
16 **Konstam MA**, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, Raval AN, Ward C; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. *Circulation* 2018; **137**: e578-e622 [PMID: 29650544 DOI: 10.1161/CIR.0000000000000560]

17 **Simioniuc A**, Carluccio E, Ghio S, Rossi A, Biagioli P, Reboldi G, Galeotti GG, Lu F, Zara C, Whalley G, Temporelli PL, Dini FL; investigators of the Network Labs Ultrasound (NEBULA) in Heart Failure Study Group. Echo and natriuretic peptide guided therapy improves outcome and reduces worsening renal function in systolic heart failure: An observational study of 1137 outpatients. *Int J Cardiol* 2016; **224**: 416-423 [PMID: 27690339 DOI: 10.1016/j.ijcard.2016.09.034]

18 **López-Candales A**, Edelman K. Shape of the right ventricular outflow Doppler envelope and severity of pulmonary hypertension. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 309-316 [PMID: 22087011 DOI: 10.1093/ejechocard/jer235]

19 **Lopez-Candales A**, Eleswarapu A, Shaver J, Edelman K, Gulyasy B, Candales MD. Right ventricular outflow tract spectral signal: a useful marker of right ventricular systolic performance and pulmonary hypertension severity. *Eur J Echocardiogr* 2010; **11**: 509-515 [PMID: 20207723 DOI: 10.1093/ejechocard/jeq009]

20 **Arkles JS**, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, Marzec L, Palevsky HI, Ferrari VA, Forfia PR. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. *Am J Respir Crit Care Med* 2011; **183**: 268-276 [PMID: 20709819 DOI: 10.1164/rccm.201004-0601OC]

21 **Brennan JM**, Blair JE, Goonewardena S, Ronan A, Shah D, Vasaiwala S, Kirkpatrick JN, Spencer KT. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. *J Am Soc Echocardiogr* 2007; **20**: 857-861 [PMID: 17617312 DOI: 10.1016/j.echo.2007.01.005]

22 **Seo Y**, Iida N, Yamamoto M, Machino-Ohtsuka T, Ishizu T, Aonuma K. Estimation of Central Venous Pressure Using the Ratio of Short to Long Diameter from Cross-Sectional Images of the Inferior Vena Cava. *J Am Soc Echocardiogr* 2017; **30**: 461-467 [PMID: 28065586 DOI: 10.1016/j.echo.2016.12.002]

23 **Jue J**, Chung W, Schiller NB. Does inferior vena cava size predict right atrial pressures in patients receiving mechanical ventilation? *J Am Soc Echocardiogr* 1992; **5**: 613-619 [PMID: 1466886 DOI: 10.1016/s0894-7317(14)80327-1]

24 **Koratala A**. Pitfalls of inferior vena cava M-mode. NephroPOCUS.com. [cited 17 June 2023]. Available from: https://nephropocus.com/2020/07/10/pitfalls-of-inferior-vena-cava-m-mode/

25 **Vaidya GN**, Kolodziej A, Stoner B, Galaviz JV, Cao X, Heier K, Thompson M, Birks E, Campbell K. Bedside ultrasound of the internal jugular vein to assess fluid status and right ventricular function: The POCUS-JVD study. *Am J Emerg Med* 2023; **70**: 151-156 [PMID: 37307660 DOI: 10.1016/j.ajem.2023.05.042]

26 **Simon MA**, Kliner DE, Girod JP, Moguillansky D, Villanueva FS, Pacella JJ. Detection of elevated right atrial pressure using a simple bedside ultrasound measure. *Am Heart J* 2010; **159**: 421-427 [PMID: 20211304 DOI: 10.1016/j.ahj.2010.01.004]

27 **Leal-Villarreal MAJ**, Aguirre-Villarreal D, Vidal-Mayo JJ, Argaiz ER, García-Juárez I. Correlation of Internal Jugular Vein Collapsibility With Central Venous Pressure in Patients With Liver Cirrhosis. *Am J Gastroenterol* 2023 [PMID: 37146133 DOI: 10.14309/ajg.0000000000002315]

28 **Murayama M**, Kaga S, Okada K, Iwano H, Nakabachi M, Yokoyama S, Nishino H, Tsujinaga S, Chiba Y, Ishizaka S, Motoi K, Kamiya K, Nishida M, Nagai T, Anzai T. Clinical Utility of Superior Vena Cava Flow Velocity Waveform Measured from the Subcostal Window for Estimating Right Atrial Pressure. *J Am Soc Echocardiogr* 2022; **35**: 727-737 [PMID: 35150833 DOI: 10.1016/j.echo.2022.02.002]

29 **Beaubien-Souligny W**, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, Denault AY. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. *Ultrasound J* 2020; **12**: 16 [PMID: 32270297 DOI: 10.1186/s13089-020-00163-w]

30 **Koratala A**, Reisinger N. Venous Excess Doppler Ultrasound for the Nephrologist: Pearls and Pitfalls. *Kidney Med* 2022; **4**: 100482 [PMID: 35707749 DOI: 10.1016/j.xkme.2022.100482]

31 **Argaiz ER**, Rola P, Gamba G. Dynamic Changes in Portal Vein Flow during Decongestion in Patients with Heart Failure and Cardio-Renal Syndrome: A POCUS Case Series. *Cardiorenal Med* 2021; **11**: 59-66 [PMID: 33477157 DOI: 10.1159/000511714]

32 **Taleb Abdellah A**, Koratala A. Nephrologist-Performed Point-of-Care Ultrasound in Acute Kidney Injury: Beyond Hydronephrosis. *Kidney Int Rep* 2022; **7**: 1428-1432 [PMID: 35685325 DOI: 10.1016/j.ekir.2022.02.017]

33 **Rihl MF**, Pellegrini JAS, Boniatti MM. VExUS Score in the Management of Patients With Acute Kidney Injury in the Intensive Care Unit: AKIVEX Study. *J Ultrasound Med* 2023 [PMID: 37310104 DOI: 10.1002/jum.16288]

34 **Turk M**, Robertson T, Koratala A. Point-of-care ultrasound in diagnosis and management of congestive nephropathy. *World J Crit Care Med* 2023; **12**: 53-62 [PMID: 37034023 DOI: 10.5492/wjccm.v12.i2.53]

35 **Sivaciyan V**, Ranganathan N. Transcutaneous doppler jugular venous flow velocity recording. *Circulation* 1978; **57**: 930-939 [PMID: 639215 DOI: 10.1161/01.cir.57.5.930]

36 **Appleton CP**, Hatle LK, Popp RL. Superior vena cava and hepatic vein Doppler echocardiography in healthy adults. *J Am Coll Cardiol* 1987; **10**: 1032-1039 [PMID: 3668102 DOI: 10.1016/s0735-1097(87)80343-1]

37 **Ghio S**, Recusani F, Sebastiani R, Klersy C, Raineri C, Campana C, Lanzarini L, Gavazzi A, Tavazzi L. Doppler velocimetry in superior vena cava provides useful information on the right circulatory function in patients with congestive heart failure. *Echocardiography* 2001; **18**: 469-477 [PMID: 11567591 DOI: 10.1046/j.1540-8175.2001.00469.x]

38 **Alimoğlu E**, Erden A, Gürsel K, Olçer T. Correlation of right atrial pressure and blood flow velocities in the common femoral vein obtained by duplex Doppler sonography. *J Clin Ultrasound* 2001; **29**: 87-91 [PMID: 11425093 DOI: 10.1002/1097-0096(200102)29:2<87::AID-JCU1003>3.0.CO;2-1]

39 **Bhardwaj V**, Rola P, Denault A, Vikneswaran G, Spiegel R. Femoral vein pulsatility: a simple tool for venous congestion assessment. *Ultrasound J* 2023; **15**: 24 [PMID: 37165284 DOI: 10.1186/s13089-023-00321-w]

40 **Mostafa A**, Said K, Ammar W, Eltawil AE, Abdelhamid M. New renal haemodynamic indices can predict worsening of renal function in acute decompensated heart failure. *ESC Heart Fail* 2020; **7**: 2581-2588 [PMID: 32602661 DOI: 10.1002/ehf2.12835]

41 **Umgelter A**, Reindl W, Franzen M, Lenhardt C, Huber W, Schmid RM. Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. *Intensive Care Med* 2009; **35**: 152-156 [PMID: 18802688 DOI: 10.1007/s00134-008-1253-y]

42 **Goyal S**, Dixit VK, Jain AK, Shukla RC, Ghosh J, Kumar V. Intrarenal resistance index (RI) as a predictor of early renal impairment in patients with liver cirrhosis. *Trop Gastroenterol* 2013; **34**: 235-239 [PMID: 25046885 DOI: 10.7869/tg.140]

43 **Deruddre S**, Cheisson G, Mazoit JX, Vicaut E, Benhamou D, Duranteau J. Renal arterial resistance in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed with Doppler ultrasonography. *Intensive Care Med* 2007; **33**: 1557-1562 [PMID: 17486316 DOI: 10.1007/s00134-007-0665-4]

44 **Di Nicolò P**, Granata A. Renal intraparenchymal resistive index: the ultrasonographic answer to many clinical questions. *J Nephrol* 2019; **32**: 527-538 [PMID: 30539416 DOI: 10.1007/s40620-018-00567-x]

45 **Chiu L**, Jairam MP, Chow R, Chiu N, Shen M, Alhassan A, Lo CH, Chen A, Kennel PJ, Poterucha TJ, Topkara VK. Meta-Analysis of Point-of-Care Lung Ultrasonography Versus Chest Radiography in Adults With Symptoms of Acute Decompensated Heart Failure. *Am J Cardiol* 2022; **174**: 89-95 [PMID: 35504747 DOI: 10.1016/j.amjcard.2022.03.022]

46 **Kocijancic I**, Vidmar K, Ivanovi-Herceg Z. Chest sonography versus lateral decubitus radiography in the diagnosis of small pleural effusions. *J Clin Ultrasound* 2003; **31**: 69-74 [PMID: 12539247 DOI: 10.1002/jcu.10141]

47 **Neighbor ML**. Ascites. *Emerg Med Clin North Am* 1989; **7**: 683-697 [PMID: 2663463]

48 **Page JE**, Morgan SH, Eastwood JB, Smith SA, Webb DJ, Dilly SA, Chow J, Pottier A, Joseph AE. Ultrasound findings in renal parenchymal disease: comparison with histological appearances. *Clin Radiol* 1994; **49**: 867-870 [PMID: 7828393 DOI: 10.1016/s0009-9260(05)82877-6]

49 **Moghazi S**, Jones E, Schroepple J, Arya K, McClellan W, Hennigar RA, O'Neill WC. Correlation of renal histopathology with sonographic findings. *Kidney Int* 2005; **67**: 1515-1520 [PMID: 15780105 DOI: 10.1111/j.1523-1755.2005.00230.x]

50 **Koratala A**, Bhattacharya D, Kazory A. Point of care renal ultrasonography for the busy nephrologist: A pictorial review. *World J Nephrol* 2019; **8**: 44-58 [PMID: 31363461 DOI: 10.5527/wjn.v8.i3.44]

51 **Nepal S**, Dachsel M, Smallwood N. Point-of-care ultrasound rapidly and reliably diagnoses renal tract obstruction in patients admitted with acute kidney injury. *Clin Med (Lond)* 2020; **20**: 541-544 [PMID: 33199317 DOI: 10.7861/clinmed.2019-0417]

52 **Pathan SA**, Mitra B, Mirza S, Momin U, Ahmed Z, Andraous LG, Shukla D, Shariff MY, Makki MM, George TT, Khan SS, Thomas SH, Cameron PA. Emergency Physician Interpretation of Point-of-care Ultrasound for Identifying and Grading of Hydronephrosis in Renal Colic Compared With Consensus Interpretation by Emergency Radiologists. *Acad Emerg Med* 2018; **25**: 1129-1137 [PMID: 29663580 DOI: 10.1111/acem.13432]

53 **Koratala A**. The Ultrasound Mimics of Hydronephrosis. Renal Fellow Network. [cited 18 June 2023]. Available from: https://www.renalfellow.org/2019/05/10/the-ultrasound-mimics-of-hydronephrosis/#:~:text=Prominent%20renal%20vasculature%20and%20vascular,also%20appears%20black%20on%20ultrasound

54 **Koratala A**, Olaoye OA, Bhasin-Chhabra B, Kazory A. A Blueprint for an Integrated Point-of-Care Ultrasound Curriculum for Nephrology Trainees. *Kidney360* 2021; **2**: 1669-1676 [PMID: 35372975 DOI: 10.34067/KID.0005082021]

55 **Koratala A**, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; **3**: 1965-1968 [PMID: 36514396 DOI: 10.34067/KID.0005522022]

World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2023 September 25; 12(4): 104-111

DOI: 10.5527/wjn.v12.i4.104

ISSN 2220-6124 (online)

SYSTEMATIC REVIEWS

Role of simulation in kidney stone disease: A systematic review of literature trends in the 26 years

Carlotta Nedbal, Victoria Jahrreiss, Clara Cerrato, Amelia Pietropaolo, Andrea Galosi, Domenico Veneziano, Panagiotis Kallidonis, Bhaskar K Somani

Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Odhar HA, Iraq; Sarier M, Turkey

Received: May 12, 2023
Peer-review started: May 12, 2023
First decision: June 1, 2023
Revised: June 7, 2023
Accepted: June 25, 2023
Article in press: June 25, 2023
Published online: September 25, 2023

Carlotta Nedbal, Victoria Jahrreiss, Clara Cerrato, Amelia Pietropaolo, Bhaskar K Somani, Department of Urology, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, United Kingdom

Andrea Galosi, Department of Urology, Azienda Ospedaliero-Universitaria delle Marche, Polytechnic University of Marche, Ancona 60121, Italy

Domenico Veneziano, Department of Urology, The Smith Institute for Urology, Northwell Health, New York, NY 11042, United States

Panagiotis Kallidonis, Department of Urology, University of Patras, Patras 26500, Greece

Corresponding author: Bhaskar K Somani, FRCS (Ed), Full Professor, Department of Urology, University Hospital Southampton NHS Trust, Tremona Road, Southampton SO16 6YD, United Kingdom. bhaskarsomani@yahoo.com

Abstract

BACKGROUND

Minimally invasive techniques for treatment of urinary stones requires expertise, experience and endoscopic skills. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities.

AIM

To report the publication trend of 'simulation in urolithiasis' over the last 26 years.

METHODS

Research of all published papers on "Simulation in Urolithiasis" was performed through PubMed database over the last 26 years, from January 1997 to December 2022. Papers were labelled and divided in three subgroups: (1) Training papers; (2) Clinical simulation application or surgical procedures; and (3) Diagnostic radiology simulation. Each subgroup was then divided into two 13-year time periods to compare and identify the contrast of different decades: period-1 (1997-2009) and period-2 (2010-2022).

RESULTS

A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: n = 94, surgical procedures: n = 66, and radiology:

n = 8). The overall number of papers published in simulation in urolithiasis was 35 in Period-1 and 129 in Period-2, an increase of +269% (P = 0.0002). Each subgroup shows a growing trend of publications from Period-1 to Period-2: training papers +279% (P = 0.001), surgical simulations +264% (P = 0.0180) and radiological simulations +200% (P = 0.2105).

CONCLUSION

In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of 3D-printed and high-fidelity models, simulation for surgical procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

Key Words: Kidney calculi; Urolithiasis; Simulation; Ureteroscopy; Percutaneous nephrolithotomy; Artificial intelligence

Core Tip: The role of simulation training in the management of kidney stones has evolved. There has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of three-dimensional printed and high-fidelity models, simulation for kidney stone procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

Citation: Nedbal C, Jahrreiss V, Cerrato C, Pietropaolo A, Galosi A, Veneziano D, Kallidonis P, Somani BK. Role of simulation in kidney stone disease: A systematic review of literature trends in the 26 years. *World J Nephrol* 2023; 12(4): 104-111
URL: https://www.wjgnet.com/2220-6124/full/v12/i4/104.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i4.104

INTRODUCTION

Minimally invasive techniques for treatment of urinary stones requiresexpertise, experience and endoscopic skills[1]. The learning curve to gain precision and accuracy in endoscopic procedures such as ureteroscopy (URS) and percutaneous nephrolithotomy (PCNL), and shockwave lithotripsy (SWL), has proven to be steep, leading to the need for training in non-operating settings[2]. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities and example of endoscopic procedures[3].

Different types of simulators can be found in the literature, with various degrees of fidelity or realism, and varying in costs[4]. Benchtop simulators are inanimate models that come cheap and are widely available, reusable and portable. Being useful for mastering the use of endoscopic instruments, these models are yet not as realistic and seem to be more appropriate for novice surgeons[5]. Realistic ex-vivo models, for example animals or human cadavers would in fact be more appropriate for advanced training, who need to master more intricate steps and advanced procedures[6].

Animal and cadaver simulators have greater costs than inanimate devices, can only be used once, and can have ethical issues[7]. The most recently developed type of simulators is based on virtual reality (VR), a computer-based simulation model that can mimic basic procedures as well as advanced interventions, being realistic and able to instantly give feedback to the trainees[8]. VR is a reusable simulator with amazing applicability but has high purchase costs and unreliable haptics.

Numerous studies have been performed on application of simulators in training of residents and expert surgeons, with focus on costs, performance, learning curve and standardized protocols[9]. As gathered from data, simulators are increasingly relied on for urology resident training worldwide[10].

Nonetheless, VR simulators, benchtop and three-dimensional (3D) printed models are now being used as tools to improve performance of endoscopic procedure in a patient-specific settings[11], for example developing a case-specific surgical planning before entering the operation theatre or simulating outcomes of different approaches. In particular, several studies reported the application for preoperative simulated puncture in complex PCNL, on different simulator models[12]. Moreover, simulators can be used to study performance and comparison of different instruments as laser fibers and their settings, endoscopic baskets or flexible scopes, without risking endangering patients in an in-vivo surgical procedure[13].

As a tool for enhancing patient-surgeon relationship and counseling, simulators have even been used to improve patient understanding of the disease and surgical procedure, resulting in higher levels of postoperative satisfaction[14].

The increasing trend of application of artificial intelligence and its subsets in the management of urolithiasis has already been investigated, with promising results[15]. It appears that the application of simulators is spreading in the urologic scientific community, from training to research and surgical planning. In this comprehensive review, we aim to report the publication trend of 'simulation in urolithiasis' over the last 26 years.

MATERIALS AND METHODS

Research of all published papers on "Simulation in Urolithiasis" was performed through PubMed database over the last 26 years, from January 1997 to Dec 2022, using MeSH terms, title words, and key words (Figure 1).

Search strategy and study selection

Cochrane methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to shape the study design[16]. All papers with relevant abstracts were identified through search on online database PubMed from 1997 to 2022.

Keywords used for searching included: "Urolithiasis", "Kidney calculi" and "Stones". MESH terms used in this screening process were: "Simulation", "Virtual Reality", "Augmented Reality" "Mixed Reality", "URS Simulation", "PCNL Simulation", "SWL Simulation", "3D printing", "Training", "Training box", "Bench Training", "Phantom" and "Bench model". All English and non-English abstracts were screened as there was no language restriction in the study. Systematic and non-systematic reviews were included in the study. Studies without a published abstract were excluded, as well as animal studies, human cadaveric studies and case reports.

After screening and extraction, papers were label according to subject: Training papers, studies on clinical applications or surgical procedures (surgical: URS, PCNL, SWL; instruments performance: Ureteral stent, scope, lithotripter, laser), studies of diagnostic (radiology) simulation on phantoms.

To better analyze the trend variation, papers were divided according to time of publication into two time periods: Period-1 (1997-2009) and Period-2 (2010-2022).

Evidence acquisition: criteria for including studies for this review

Inclusion criteria: All English language studies with a published abstract; All non-English studies with abstracts published in the English language; Studies reporting on simulation in urolithiasis: Training simulations with box simulators, phantoms for both diagnostic and therapeutic procedures; Simulations device for surgical planning (URS, PCNL, SWL) and patient-specific simulation; Studies of surgical performance using simulators (scopes, ureteral stents, laser fibers, lithotripters).

Exclusion criteria: Studies without a published abstract; Studies for non-urolithiasis conditions; Studies on human cadavers or animals; Case reports and meeting abstracts.

Two authors (C.N., V.J.) independently performed a literature search to identify studies and discrepancies were resolved after input and discussion with the senior author (B.K.S). Extracted articles on simulation were then divided in three subgroups according to field of interest: (1) Training; (2) Clinical application; and (3) Radiology simulation (Figure 2). Each subgroup was then divided into two 13-year time periods to compare and identify the contrast of different decades: Period-1 (1997-2009) and Period-2 (2010-2022).

Data were collected using Microsoft Excel (version 2007), analyzed through the independent *t* test. A statistically significant threshold level was stated at $P < 0.05$ to rule out possible difference in the data collected form Period-1 *vs* Period-2.

RESULTS

Overall number of papers

A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: $n = 94$, surgical procedures: $n = 66$, and radiology: $n = 8$). 164 papers were published in English; only 4 articles had an English language abstract and a non-English full paper: 1 in Chinese, 1 in French, and 2 in Russian.

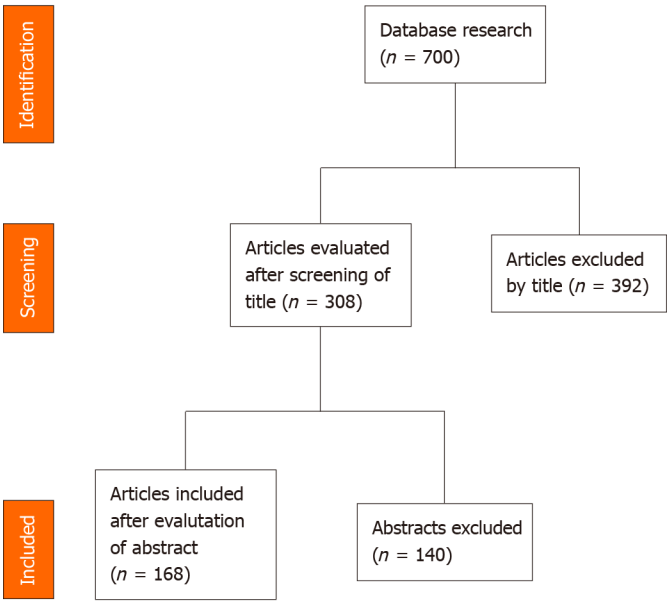
For training procedures, articles included URS training ($n = 53$), PCNL training ($n = 22$) or simulation training for both these procedures ($n = 19$). Clinical application of simulation in surgical procedures included articles on URS ($n = 29$), PCNL ($n = 26$), SWL ($n = 5$) and ureteral stenting ($n = 6$). Regarding radiological simulations with phantoms, articles were found with application on diagnostic procedures ($n = 5$) and intraoperative imaging features ($n = 3$).

The overall number of papers published in simulation in urolithiasis was 35 in Period-1 and 129 in Period-2, with a significant increase of +269% ($P = 0.0002$). Each subgroup shows a growing trend of publications from Period-1 to Period-2: training papers +279% ($P = 0.001$), surgical simulations +264% ($P = 0.0180$) and radiological simulations +200% ($P = 0.2105$).

Training simulation papers

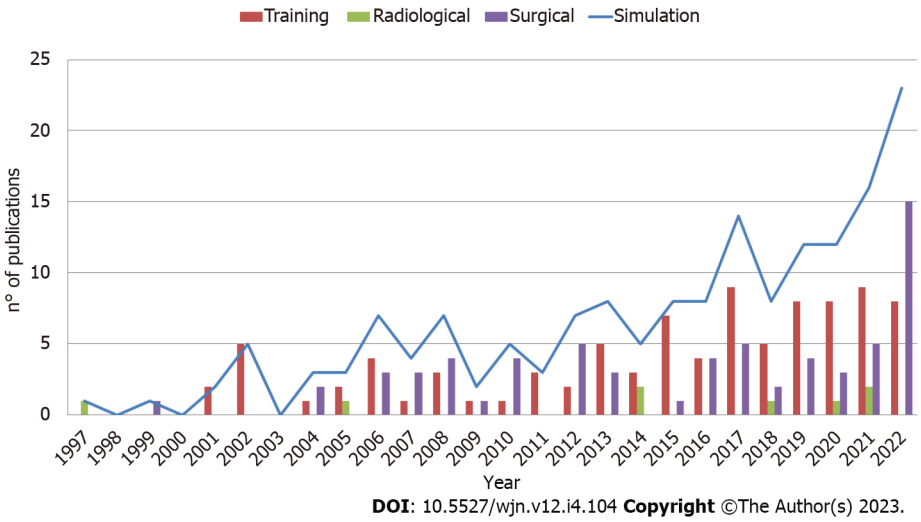
Of the 94 papers on simulation for training in endourology, 72 were published in Period-2, accounting for more than 76% of current publications.

Analysis of application of simulators for URS ($n = 51$) shows a significant rise by +225% ($P = 0.0016$) in Period-2. Similarly, simulation papers on PCNL training ($n = 21$) had a steep increase of +850% ($P = 0.0023$) in Period-2. Looking at simulations with a mixed setting with both URS and PCNL procedures, the rise by +180% was not statistically significant ($P = 0.1275$). In this research, 11 reviews were found, with great interest in residents' training with simulators, assessing learning curves and developing standardized protocols of training. In the last 5 years, from 2018 to 2022, the numbers of papers on training with simulation for URS, PCNL and mixed endourological training were 17, 11 and 10 papers respectively.



DOI: 10.5527/wjn.v12.i4.104 **Copyright** ©The Author(s) 2023.

Figure 1 PRISMA flowchart of the included studies.



DOI: 10.5527/wjn.v12.i4.104 **Copyright** ©The Author(s) 2023.

Figure 2 Trend of publications on 'Simulation in Urolithiasis' (trend line), with different subgroup as Training, Surgical and Radiological simulation.

Surgical simulation papers

Publication trend on surgical application of simulators in endourology has increased significantly (P = 0.0180) from Period-1 to period-2 (+264%), with 14 and 51 papers respectively.

Analysis of those papers found varied topics from application of patient-specific simulators (benchtop, 3D printed models, VR simulators) for surgical planning both in URS and PCNL, simulators of SWL (phantoms, VR) for predicting performance of lithotripsy, analysis of stent features in 3D models, evaluation of procedural instrumentation such as scopes, lasers, lithotripters and endoscopic baskets during surgical procedures (URS and PCNL).

Papers on simulations in URS (n = 28) rose significantly in Period-2 (+360%, P = 0.0039), PCNL simulations (n = 26) increased too (+1100%, P = 0.0181). SWL simulation and ureteral stent simulation on the other had reduced in period-2 (-33%, P = 0.6983 and -50%, P = 0.5912 respectively).

Radiological simulation papers

Application of simulators in radiology differed in our results from a diagnostic setting (preoperative), with phantoms used as tools to test efficiency of examinations, to a surgical setting (intraoperative), assessing quality of imaging and reconstructions. These increased from period-1 (n = 2) to period-2 (n = 6), a rise by +200% (P = 0.2105).

DISCUSSION

The role of simulation devices has been widely analyzed in the last decades, with particular attention to its application for training and assessment. Different studies have been proposed to rule out the efficacy in teaching residents' surgical skills in a non-operative setting, mostly with the aim to improve patient safety and reduce harm, while allowing a safe pre-surgical exposure to trainees[17]. The possibility to experiment difficult steps of endoscopic procedure, surgery that requires high level of training and experience, has been in fact a blessing in disguise[18]. The role of simulation in easing the learning curve of trainees has been positively reported, as well as its impact in leading the residents through difficult procedures in a low-stress setting[19].

Protocolshave then been developed to standardize resident training in a more efficient way[20], proposing different steps of expertise and accuracy, sometimes even with the aid of different simulators based on their grade of fidelity and accuracy[21].

What emerges from literature is that simulation can play a game-changing role in training. Its applications are almost infinite, ranging from easier procedure such as cystoscopic examination[22] and ureteral stent insertion, through to gain accuracy with complex procedures such as flexible URS and PCNL. Some models have even been developed to simulate unexpected scenarios like ureteral strictures, kinking and complications[23]. This allows trainees to get experience in more advanced scenarios without putting patients at risk.

Not every aspect of simulator training is perfect and even the more modern and technological simulators (VR for example) often lack enough realistic sensibility to train the haptics, and the absence of stress in a simulated environment can be misleading in the training process and may not allow trainees to deal with unexpected events[24].

There is an increasing trend of the use of simulators and simulation training over the last decade, and it is difficult to ignore the leading role simulators are playing in surgical improvement[10]. Our research found numerous papers on the application of simulation devices, especially phantoms and 3D printed models, for testing new technological devices.

In the studies regarding URS, laser fibers were tested to understand the effect different settings had on the stones or soft tissue, comparing different baskets and smaller scopes[25]. In PCNL simulation, the main focus emerged in the planning of renal puncture with accuracy and without perforation of neighboring structures[26]. To this aim, several studied have been performed in a patient-specific setting with realistic 3D-printed models[27]. As this review found out, the role of SWL in stone treatment has become progressively confined with only few papers found on application of simulation for SWL, for example analyzing gel propertiesor stone disruption, and none of them has been published in the last 10 years[28].

Development of 3D-printed models and VR has also been used in literature as an aid to counsel patients. Anatomically accurate models can influence the understanding of a patient's own disease, along with the surgical procedure, the possible complications and outcomes[29]. Recent studies have in fact pointed out the positive correlation that lies between the use of simulators in patient counseling and their overall satisfaction, with a positive role on surgeon-patient relationship and for avoiding misunderstandings[30]. This relatively new application of simulation could gain an important role in daily clinical practice.

Simulation based curriculum is now endorsed by the European Association of Urology (EAU) and European School of Urology (ESU)[31]. Other educational articles will help reinforce the training perspective to trainees[32]. There also seems to be an increasing role of artificial intelligence for training and education[33].

Strengths and weakness of bibliometric trend analysis

In this review, the first to our knowledge to evaluate the trend of publication of simulation in urolithiasis over the last 26 years, we aimed to report a comprehensive scenario of current literature. Both English and non-English language studies have been included in this review. On the other hand, the authors are aware that limiting our research to PubMed database, some articles published in non-index journals might have been missed. We consider though this to be a minor limitation, as bibliographic accuracy should still be obtained from this database alone[34]. This review is intended to analyze publication trends on simulation in the management of urolithiasis, and it does not just include training or clinical papers[35,36], but all studies performed with the application of simulators in endourology.

CONCLUSION

This review found an increasing bibliometric publication trend on the application of simulators in endourological practice. In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of 3D-printed and high-fidelity models, simulation for surgical procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

ARTICLE HIGHLIGHTS

Research background

Minimally invasive techniques for treatment of urinary stones requires expertise, experience and endoscopic skills. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities.

Research motivation
To report the publication trend of 'simulation in urolithiasis' over the last 26 years.

Research objectives
To analyze the simulation trends over the last 26 years.

Research methods
Research of all published papers on "Simulation in Urolithiasis" over the last 26 years: (1) Training papers; (2) Clinical simulation application or surgical procedures; and (3) Diagnostic radiology simulation. Data was further analyzed in two 13-year time periods to compare and identify the contrast of different decades: Period-1 (1997-2009) and period-2 (2010-2022).

Research results
A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: n = 94, surgical procedures: n = 66, and radiology: n = 8). The overall number of papers published in simulation in urolithiasis increased over time for all three areas with more simulation based studies in the last decade.

Research conclusions
In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs.

Research perspectives
Simulation trends could guide future researchers on training and safe surgical practice patterns.

FOOTNOTES

Author contributions: Nedbal C contributed to writing; Nedbal C and Jahrreiss V contributed to data collection; Cerrato C contributed to data analysis; Pietropaolo A, Galosi AB, Veneziano D, Kallidonis P, and Somani BK contributed to editing; Somani BK contributed to conceptualization and coordintation.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: United Kingdom

ORCID number: Bhaskar K Somani 0000-0002-6248-6478.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Brunckhorst O**, Aydin A, Abboudi H, Sahai A, Khan MS, Dasgupta P, Ahmed K. Simulation-based ureteroscopy training: a systematic review. *J Surg Educ* 2015; **72**: 135-143 [PMID: 25130385 DOI: 10.1016/j.jsurg.2014.07.003]
2 **Ng CF**. Training in percutaneous nephrolithotomy: The learning curve and options. *Arab J Urol* 2014; **12**: 54-57 [PMID: 26019924 DOI: 10.1016/j.aju.2013.08.002]
3 **Sarmah P**, Voss J, Ho A, Veneziano D, Somani B. Low vs. high fidelity: the importance of 'realism' in the simulation of a stone treatment procedure. *Curr Opin Urol* 2017; **27**: 316-322 [PMID: 28403125 DOI: 10.1097/MOU.0000000000000401]
4 **Pelly T**, Shanmugathas N, Bowyer H, Wali A, Pankhania R. Low-cost simulation models in Urology: a systematic review of the literature. *Cent European J Urol* 2020; **73**: 373-380 [DOI: 10.5173/ceju.2020.0122]
5 **Matsumoto ED**, Hamstra SJ, Radomski SB, Cusimano MD. The effect of bench model fidelity on endourological skills: a randomized controlled study. *J Urol* 2002; **167**: 1243-1247 [DOI: 10.1016/S0022-5347(05)65274-3]
6 **Bowling CB**, Greer WJ, Bryant SA, Gleason JL, Szychowski JM, Varner RE, Holley RL, Richter HE. Testing and validation of a low-cost cystoscopy teaching model: a randomized controlled trial. *Obstet Gynecol* 2010; **116**: 85-91 [PMID: 20567172 DOI: 10.1097/AOG.0b013e3181e45a52]

7 **Hameed BMZ**, Somani S, Keller EX, Balamanigandan R, Mahapatra S, Pietropaolo A, Tonyali Ş, Juliebø-Jones P, Naik N, Mishra D, Kumar S, Chlosta P, Somani BK. Application of Virtual Reality, Augmented Reality, and Mixed Reality in Endourology and Urolithiasis: An Update by YAU Endourology and Urolithiasis Working Group. *Front Surg* 2022; **9**: 866946 [PMID: 35433825 DOI: 10.3389/fsurg.2022.866946]

8 **Aydın A**, Baig U, Al-Jabir A, Sarıca K, Dasgupta P, Ahmed K. Simulation-Based Training Models for Urolithiasis: A Systematic Review. *J Endourol* 2021; **35**: 1098-1117 [PMID: 33198492 DOI: 10.1089/end.2020.0408]

9 **Aditya I**, Kwong JCC, Canil T, Lee JY, Goldenberg MG. Current Educational Interventions for Improving Technical Skills of Urology Trainees in Endourological Procedures: A Systematic Review. *J Endourol* 2020; **34**: 723-731 [PMID: 31691593 DOI: 10.1089/end.2019.0693]

10 **Hameed BMZ**, Pietropaolo A, Naik N, Noronha C, Juliebø-Jones P, Mykoniatis I, Esperto F, Shah M, Ibrahim S, Shetty DK, Karimi H, Sharma D, Rai BP, Chlosta P, Somani BK. Role of three dimensional (3D) printing in endourology: An update from EAU young academic urologists (YAU) urolithiasis and endourology working group. *Front Surg* 2022; **9**: 862348 [PMID: 36061049 DOI: 10.3389/fsurg.2022.862348]

11 **Hameed BMZ**, Shah M, Pietropaolo A, De Coninck V, Naik N, Skolarikos A, Somani BK. The technological future of percutaneous nephrolithotomy: a Young Academic Urologists Endourology and Urolithiasis Working Group update. *Curr Opin Urol* 2023; **33**: 90-94 [PMID: 36622261 DOI: 10.1097/MOU.0000000000001070]

12 **Favorito LA**. Kidney anatomy: three dimensional (3D) printed pelvicalyceal system models of the collector system improve the diagnosis and treatment of stone disease. *Int Braz J Urol* 2017; **43**: 381-382 [PMID: 28520334 DOI: 10.1590/S1677-5538.IBJU.2017.03.01]

13 **Ventimiglia E**, Sindhubodee S, Besombes T, Pauchard F, Quadrini F, Delbarre B, Jiménez Godínez A, Barghouthy Y, Corrales Acosta MA, Kamkoum H, Villa L, Doizi S, Somani BK, Traxer O. Operator-assisted vs self-achieved basketing during ureteroscopy: results from an in vitro preference study. *World J Urol* 2021; **39**: 2169-2175 [PMID: 33025141 DOI: 10.1007/s00345-020-03431-5]

14 **Bergmeister KD**, Aman M, Kramer A, Schenck TL, Riedl O, Daeschler SC, Aszmann OC, Bergmeister H, Golriz M, Mehrabi A, Hundeshagen G, Enkhbaatar P, Kinsky MP, Podesser BK. Simulating Surgical Skills in Animals: Systematic Review, Costs & Acceptance Analyses. *Front Vet Sci* 2020; **7**: 570852 [PMID: 33195561 DOI: 10.3389/fvets.2020.570852]

15 **Pietropaolo A**, Proietti S, Geraghty R, Skolarikos A, Papatsoris A, Liatsikos E, Somani BK. Trends of 'urolithiasis: interventions, simulation, and laser technology' over the last 16 years (2000-2015) as published in the literature (PubMed): a systematic review from European section of Uro-technology (ESUT). *World J Urol* 2017; **35**: 1651-1658 [PMID: 28593477 DOI: 10.1007/s00345-017-2055-z]

16 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535 [PMID: 19622551 DOI: 10.1136/bmj.b2535]

17 **Skolarikos A**, Gravas S, Laguna MP, Traxer O, Preminger GM, de la Rosette J. Training in ureteroscopy: a critical appraisal of the literature. *BJU Int* 2011; **108**: 798-805; discussion 805 [PMID: 21884354 DOI: 10.1111/j.1464-410X.2011.10337.x]

18 **Villa L**, Somani BK, Sener TE, Cloutier J, ButticèF, Marson F, Ploumidis A, Proietti S, Traxer O. Comprehensive flexible ureteroscopy (FURS) simulator for training in endourology: The K-box model. *Cent European J Urol* 2016; **69**: 118-120 [DOI: 10.5173/ceju.2016.710]

19 **Matsumoto ED**, Pace KT, D'A Honey RJ. Virtual reality ureteroscopy simulator as a valid tool for assessing endourological skills. *Int J Urol* 2006; **13**: 896-901 [PMID: 16882051 DOI: 10.1111/j.1442-2042.2006.01436.x]

20 **Aydın A**, Ahmed K, Baig U, Raison N, Lantz Powers AG, Macchione N, Al-Jabir A, Abe T, Khan MS, Dasgupta P; SIMULATE Trial Contributors. The SIMULATE ureteroscopy training curriculum: educational value and transfer of skills. *World J Urol* 2021; **39**: 3615-3621 [PMID: 33533996 DOI: 10.1007/s00345-021-03604-w]

21 **Schout BM**, Hendrikx AJ, Scherpbier AJ, Bemelmans BL. Update on training models in endourology: a qualitative systematic review of the literature between January 1980 and April 2008. *Eur Urol* 2008; **54**: 1247-1261 [PMID: 18597924 DOI: 10.1016/j.eururo.2008.06.036]

22 **Watterson JD**, Denstedt JD. Ureteroscopy and cystoscopy simulation in urology. *J Endourol* 2007; **21**: 263-269 [PMID: 17444769 DOI: 10.1089/end.2007.9982.A]

23 **Li D**, Suarez-Ibarrola R, Choi E, Jeong M, Gratzke C, Miernik A, Fischer P, Qiu T. Soft Phantom for the Training of Renal Calculi Diagnostics and Lithotripsy. *Annu Int Conf IEEE Eng Med Biol Soc* 2019; **2019**: 3716-3719 [DOI: 10.1109/EMBC.2019.8856426]

24 **Baker BG**, Bhalla A, Doleman B, Yarnold E, Simons S, Lund JN, Williams JP. Simulation fails to replicate stress in trainees performing a technical procedure in the clinical environment. *Med Teach* 2017; **39**: 53-57 [PMID: 27631579 DOI: 10.1080/0142159X.2016.1230188]

25 **So WZ**, Gauhar V, Chen K, Lu J, Chua WJ, Tiong HY. An in vitro Comparative Assessment of Single-Use Flexible Ureteroscopes Using a Standardized Ureteroscopy Training Model. *Urol Int* 2022; **106**: 1279-1286 [PMID: 35709703 DOI: 10.1159/000525246]

26 **Checcucci E**, Amparore D, Volpi G, Piramide F, De Cillis S, Piana A, Alessio P, Verri P, Piscitello S, Carbonaro B, Meziere J, Zamengo D, Tsaturyan A, Cacciamani G, Rivas JG, De Luca S, Manfredi M, Fiori C, Liatsikos E, Porpiglia F. Percutaneous puncture during PCNL: new perspective for the future with virtual imaging guidance. *World J Urol* 2022; **40**: 639-650 [PMID: 34468886 DOI: 10.1007/s00345-021-03820-4]

27 **de la Rosette JJ**, Laguna MP, Rassweiler JJ, Conort P. Training in percutaneous nephrolithotomy--a critical review. *Eur Urol* 2008; **54**: 994-1001 [PMID: 18394783 DOI: 10.1016/j.eururo.2008.03.052]

28 **Mendez-Probst CE**, Vanjecek M, Razvi H, Cadieux PA. Ordnance gelatine as an in vitro tissue simulation scaffold for extracorporeal shock wave lithotripsy. *Urol Res* 2010; **38**: 497-503 [PMID: 20967432 DOI: 10.1007/s00240-010-0329-7]

29 **Choi YH**, Lee SJ, Kim HY. Effect of a three-dimensional (3D) printed kidney model on patient understanding of the percutaneous nephrolithotomy procedure: a preliminary study. *Urolithiasis* 2022; **50**: 375-380 [PMID: 35122486 DOI: 10.1007/s00240-022-01308-3]

30 **Atalay HA**, Canat HL, Ülker V, Alkan İ, Özkuvanci Ü, Altunrende F. Impact of personalized three-dimensional -3D- printed pelvicalyceal system models on patient information in percutaneous nephrolithotripsy surgery: a pilot study. *Int Braz J Urol* 2017; **43**: 470-475 [PMID: 28338309 DOI: 10.1590/S1677-5538.IBJU.2016.0441]

31 **Veneziano D**, Ahmed K, Van Cleynenbreugel B, Gozen A, Palou J, Sarica K, Liatsikos E, Sanguedolce F, Honeck P, Alvarez-Maestro M, Papatsoris A, Kallidonis P, Greco F, Breda A, Somani BK. Development Methodology of the Novel Endoscopic Stone Treatment Step 1 Training/Assessment Curriculum: An International Collaborative Work by European Association of Urology Sections. *J Endourol* 2017; **31**: 934-941 [PMID: 28693386 DOI: 10.1089/end.2017.0248]

32 **Somani BK**, Aboumarzouk O, Srivastava A, Traxer O. Flexible ureterorenoscopy: Tips and tricks. *Urol Ann* 2013; **5**: 1-6 [PMID: 23662000 DOI: 10.4103/0974-7796.106869]

33 **Shah M**, Naik N, Somani BK, Hameed BMZ. Artificial intelligence (AI) in urology-Current use and future directions: An iTRUE study. *Turk J Urol* 2020; **46**: S27-S39 [PMID: 32479253 DOI: 10.5152/tud.2020.20117]

34 **Zhao X**, Jiang H, Yin J, Liu H, Zhu R, Mei S, Zhu CT. Changing trends in clinical research literature on PubMed database from 1991 to 2020.

Eur J Med Res 2022; **27**: 95 [PMID: 35725647 DOI: 10.1186/s40001-022-00717-9]

35 **Jones P**, Elmussareh M, Aboumarzouk OM, Mucksavage P, Somani BK. Role of Minimally Invasive (Micro and Ultra-mini) PCNL for Adult Urinary Stone Disease in the Modern Era: Evidence from a Systematic Review. *Curr Urol Rep* 2018; **19**: 27 [PMID: 29516304 DOI: 10.1007/s11934-018-0764-5]

36 **Whitehurst L**, Jones P, Somani BK. Mortality from kidney stone disease (KSD) as reported in the literature over the last two decades: a systematic review. *World J Urol* 2019; **37**: 759-776 [PMID: 30151599 DOI: 10.1007/s00345-018-2424-2]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com