ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2023 March 25; 12(2): 21-39

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Bimonthly Volume 12 Number 2 March 25, 2023

MINIREVIEWS

World Journal of Nephrology

Bimonthly Volume 12 Number 2 March 25, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Priyank Yadav, MBBS, MCh, MS, Assistant Professor, Surgeon, Urology and Renal Transplantation, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, Uttar Pradesh, India. priyankmamc@gmail.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
Ying-Yong Zhao, Li Zuo

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

PUBLICATION DATE
March 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 March 25; 12(2): 21-28

DOI: 10.5527/wjn.v12.i2.21

ISSN 2220-6124 (online)

MINIREVIEWS

Kidney stone matrix proteins: Role in stone formation

Armando Luis Negri, Francisco Rodolfo Spivacow

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): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ali A, Iraq; Bozkurt M, Turkey; Marickar F, India

Received: October 18, 2022
Peer-review started: October 18, 2022
First decision: December 26, 2022
Revised: January 18, 2023
Accepted: March 17, 2023
Article in press: March 17, 2023
Published online: March 25, 2023

Armando Luis Negri, Department of Physiology and Biophysics, Universidad del Salvador, Instituto de Investigaciones Metabólicas, Buenos Aires 1012, Argentina

Francisco Rodolfo Spivacow, Department of Nephrology, Instituto de Investigaciones Metabólicas, Buenos Aires 1012, Argentina

Corresponding author: Armando Luis Negri, FACP, MD, Academic Editor, Professor, Department of Physiology and Biophysics, Universidad del Salvador, Instituto de Investigaciones Metabólicas, Libertad 836 1 Piso, Buenos Aires 1012, Argentina.
negri@casasco.com.ar

Abstract

Stone formation is induced by an increased level of urine crystallization promoters and reduced levels of its inhibitors. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds such as glycosaminoglycans. In the urine, there are various proteins, such as uromodulin (Tamm-Horsfall protein), calgranulin, osteopontin, bikunin, and nephrocalcin, that are present in the stone matrix. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium and could potentially protect against lithiasis. Proteins are the most abundant component of kidney stone matrix, and their presence may reflect the process of stone formation. Many recent studies have explored the proteomics of urinary stones. Among the stone matrix proteins, the most frequently identified were uromodulin, S100 proteins (calgranulins A and B), osteopontin, and several other proteins typically engaged in inflammation and immune response. The normal level and structure of these macromolecules may constitute protection against calcium salt formation. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances. Many of these proteins have other functions in modulating oxidative stress, immune function, and inflammation that could also influence stone formation. Yet, the role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and non-stone formers.

Key Words: Stone formation; Kidney stone; Matrix proteins; Uromodulin; Calgranulin; Proteomics

Core Tip: Several urinary proteins have been found in kidney stone matrix. *In vitro* and *in vivo* studies have shown that they have an important role in various processes of calcium oxalate crystallization. Many of them have other functions in modulating oxidative stress, immune response, and inflammation that could also influence stone formation. Yet, the exact role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and non-stone formers.

Citation: Negri AL, Spivacow FR. Kidney stone matrix proteins: Role in stone formation. *World J Nephrol* 2023; 12(2): 21-28
URL: https://www.wjgnet.com/2220-6124/full/v12/i2/21.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i2.21

INTRODUCTION

Healthy people regularly excrete calcium oxalate crystals in urine. Calcium oxalate stones are formed only in a small part of the population[1]. Stones develop from crystals that form in the urine, which contains a mixture of ions, salts, macromolecules, and metabolites[2]. Crystals undergo different stages (nucleation, growth, and aggregation) until they produce a stone.

Induction of stone formation is produced by an increased level of crystallization promoters in the urine and reduced levels of its inhibitors[3]. Crystallization promoters are those substances that may constitute the crystals by which stones are formed, in particular calcium and oxalate. Idiopathic hypercalciuria is probably the principal condition underlying stone formation that produces increased levels of urinary calcium[4]. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds produced by renal tubular epithelial cells as glycosaminoglycans. Several proteins, such as uromodulin [UMOD; Tamm-Horsfall protein (THP)], calgranulin, osteopontin (OPN), bikunin, and nephrocalcin (NC), are present in the urine[5]. These proteins that are frequently found in the kidney stone matrix will be the subject of this review (Table 1).

MACROMOLECULES AND CRYSTALLIZATION

We do not know the exact role of many macromolecules present in urine in calcium salt crystallization. The normal level and structure of these macromolecules may constitute protection against formation of large, intratubular precipitates of calcium salts. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances (for example urine pH).

Back in the 1970's, Gill *et al*[7] showed an inhibitory effect of macromolecules from human urine on crystallization of calcium oxalate[6]. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium[7]. The findings showed that macromolecules could potentially protect against lithiasis and that affected patients with lithiasis may have a different composition from that in healthy subjects.

Among macromolecules, proteins are present in all stones in a slight proportion, commonly < 5%. Several proteins rich in the urine proteome, have been examined in relation to their possible role in renal lithiasis. The most abundant component of kidney stone matrix are proteins, and their presence indirectly shows the process of stone formation. Urinary stones proteomics has been analyzed in several studies[5,8-10]. In a recent study, Kaneko *et al*[11] conducted a bioinformatic research on the proteomics of urinary stones to identify the most frequent stone matrix proteins present and afterwards performed immunohistochemistry to detect the top five of those matrix proteins expressed in renal tissue. Among the stone matrix proteins, the most frequently identified were UMOD, S100 proteins (calgranulins A and B), OPN, and several other proteins that participate in inflammation and immune response. Several proteins determined by immunohistochemistry in kidney stones showed increased expression, such as S100A8, S100A9 (calgranulins A and B), and OPN, while others such as UMOD decreased. Proteomic analysis of exosomes from kidney stone patients also showed higher expression of S100 proteins[12] while they were difficult to detect in urine.

Uromodulin

UMOD, originally known as THP, is a kidney-specific protein synthesized at the thick ascending limb of the loop of Henle[13,14]. Nearly 100 mg of this protein is excreted daily, and it is the most abundant of all urinary proteins. UMOD is a complex protein with several domains including a zona pellucida domain, essential for protein polymerization, and a special anchoring domain[15]. It is composed of 640 amino acids with 48 cysteine residues that form 24 disulphide bonds and glycosylation accounts for

Table 1 Kidney stone matrix proteins as modulators of crystallization

Matrix protein name	Primary function	Celular origin	Secondary function	Mol. weight (KDal)
Uromodulin	Inhibits crystal aggregation	Epithelial cells of the TALH	Reduces local oxidative stress	87
Calgranulins	Inhibit crystal growth and aggregation	Cells of myeloid origin	Participate in innate immuneresponse	10.9-13.2
Osteopontin	Inhibits/Enhances crystal formation and aggregation	Distal tubular epithelial cells	Regulator of immune response	14
Bikunin	Inhibits crystal nucleation, growth, and aggregation	Proximal tubules and the thin descending segment	Inhibition of the action of many serine proteinases	39
Nephrocalcin	Inhibit crystal nucleation, growth, and aggregation	Proximal tubule epithelial cells and TALH	None	18

TALH: Thick ascending limb of Henle.

nearly 30% of its molecular weight. UMOD monomers are produced by epithelial cells present in the thick ascending limb of the Henle loop and then transported and secreted at both cell surfaces. At the apical surface, it is cleaved and released to the tubular fluid. Polymerization occurs depending on the physiological conditions in the urine. Putative functions of this protein include the modulation of salt and water transport, prevention of kidney stone formation by binding calcium oxalate crystals, and defense against urinary tract infection[15]. The role of UMOD in health and disease has been provided by the study of genetic diseases caused by mutations in the *UMOD* gene[16].

Measurements of THP in kidney stone formers and healthy subjects have shown decreased urinary THP in stone formers[17,18]. Urinary excretion of calcium and oxalate ions positively correlates with urinary THP in controls but not in stone formers. Only calcium stone formers show a reduction in THP. More recently, Fraser *et al*[19] studied UMOD level in urine of children with stone disease. They did not observe differences in concentration of the protein excreted between the group with symptomatic lithiasis, the group endangered with lithiasis, and the control group. In another study in children, those with lithiasis had increased UMOD excretion[20]. Similarly, increased excretion of this protein, with its different composition at the same time, was observed by Jaggi *et al*[21] in urine of affected adults with high intensity of stone formation. Possible determinants of urinary THP excretion in kidney stone formers and control subjects were studied by Glauser *et al*[22], assessing 24-h THP excretion and expressing results in the form of THP/creatinine ratio. They found that in both controls and stone formers, urinary THP excretion was related to body size, renal function, and urinary citrate excretion, whereas THP excretion was not correlated with age, urine volume, or dietary habits (dietary calcium supply or protein consumption). An increase in THP in response to increasing urinary calcium and oxalate concentrations was seen only in controls, whereas this self-protective mechanism was absent in stone formers. Therefore, the different publications presenting quantitative differences in UMOD excretion did not have the same findings, which may indicate a random nature of the differences.

Other authors have found that UMOD structure is different between persons with and without kidney stones. Stone formers had lower protein content (32%), sialic acid content (27%), and amino sugar content (nearly 20%)[23]. Viswanathan *et al*[24] have shown that UMOD contains less sialic acid in patients with lithiasis, which leads to reduction of its negative charge. This form of protein promotes aggregation of calcium oxalate monohydrate, whereas the same protein prevents aggregation in healthy subjects with a normal content of sialic residues. Thus, not only UMOD levels but also differences in THP biochemical structure may influence the development of calcium nephrolithiasis.

To better understand the *in vivo* role of THP in kidney stone formation, Mo *et al*[25] inactivated the *THP* gene[25]. The resultant *THP*$^{-/-}$ mice had no THP expression in the kidney. Intratubular crystal aggregates were seen in the collecting ducts at the inner medulla and renal papillae in these mice, while wild type littermates had no crystal deposition in the kidney. This papillary interstitial calcinosis of the THP$^{-/-}$ mice is very similar to Randall's plaques seen in calcium oxalate stone formers, but ureteral stones have been found in this model[26].

Reactive oxygen species (ROS) and inflammation have a critical role in the pathogenesis of kidney stones[27]. ROS production increases when renal tubular cells are exposed to different type of crystals, leading to epithelial cell injury[28] and release of inflammatory mediators[29]. THP$^{-/-}$ mouse kidneys have increased ROS accumulation in the kidney, particularly in the S3 segment of the proximal tubules [30]. Targeted proteomic analysis on S3 proximal epithelial cells in these mice showed that free radical scavenging proteins were at the top of the proteins that were differentially downregulated in THP$^{-/-}$ mice[30]. Thus, it is possible that one of the mechanisms by which UMOD prevents renal lithiasis is through reducing local oxidative stress.

S100 proteins (calgranulins)

S100 proteins constitute a family of calcium-binding proteins present in the cytosol, characterized by their dissolution in 100% ammonium sulphate[31]. Several of them have been classified as danger–associated molecular patterns (DAMPs) of endogenous origin, including S100A7[32], S100A8, S100A9, and S100A12[31,33]. DAMPs, also known as alarmins, are a group of endogenous intracellular molecules characterized by multiple functions, and they are generally released as inflammatory signal mediators after cell death[34].

S100A8 and S100A9 are also known as calgranulins A and B, respectively. They are constitutively expressed and produced by cells of myeloid origin, such as neutrophils and monocytes[35], and dendritic cells[36]. In other cell types, they can be induced upon activation. S100A8 and S100A9 constitute nearly half of all cytosolic proteins in neutrophils, but only 1% in monocytes[35]. S100A8 and S100A9 in the presence of zinc and calcium ions form a heterodimer called calprotectin that promotes phagocyte migration by polymerization and stabilization of tubulin microfilaments in a calcium dependent manner[37].

Toll-like receptor 4 (TLR4) and RAGE (the receptor for advanced glycation end products) are thought to be the innate immune receptors of calgranulin[38,39]. Upon binding, TLR4 signaling is triggered, which is mediated by MyD88, thus leading to NF-kB activation and secretion of pro-inflammatory cytokines[40,41]. Interaction of calgranulin with TLR4 has been shown to be involved in the pathogenesis of autoimmune diseases, systemic infections, malignancy, and acute coronary syndrome[42-45].

Momohara *et al*[46] showed the ability of calgranulins to inhibit crystallization, aggregation, and adhesion to the urinary epithelium of calcium oxalate monohydrate crystals. Mushtaq *et al*[47] also observed the presence of calgranulin in CaOx deposits but it promoted crystal aggregation. Bergsland *et al*[48] observed that the concentration and composition of calgranulin differed in subjects with a family history of urinary tract lithiasis in comparison with a healthy population. In children with stone disease, no statistically significant difference in calgranulin urine concentrations was observed between the study and control groups.

Osteopontin

OPN, also known as secreted phosphoprotein 1 (SPP-1), is a highly phosphorylated, strongly anionic glycophosphoprotein, with a molecular weight that ranges between 41 and 75 kDa, composed of 314 amino acids[49,50]. OPN was originally discovered in bone, as a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of proteins, implicated in bone mineralization and remodeling[51]. OPN suffers multiple post-translational changes that modify the OPN responses in several tissues[50,52].

In addition to bone metabolism, OPN can regulate the immune response through interactions with multiple surface proteins localized in its target cells: Macrophages, dendritic cells, and T cells. Indeed, this protein has chemotactic properties on these cells[50]. Integrin receptor binding to OPN activates the intracellular nuclear factor kappa B (NF-kB)[53]. OPN is also able to stimulate T-cell chemotaxis and adhesion, and it inhibits interleukin (IL)-10 release by macrophages[53]. In the kidney, OPN is produced and secreted into the urine by distal tubular renal epithelial cells, becoming a normal macromolecular constituent of the kidney[54].

Multiple observations support the concept that OPN may play an important role in modulating renal stone formation, such as: (1) OPN is one of the protein components of renal stone matrix[11]; (2) OPN can regulate the renal calcification process[55]; (3) OPN renal expression is altered in hyperoxaluric rats and urinary levels are changed in human subjects with urolithiasis[56]; (4) *In vitro* cell culture based studies and *in vivo* OPN knockout animal models suggest an important role of OPN in various phases of renal stone formation[57-59]; and (5) *OPN* polymorphisms have shown association with urolithiasis in different ethnic groups in candidate gene association studies[60,61].

Bikunin

Bikunin is a small chondroitin sulfate proteoglycan with a single glycosaminoglycan chain. It is the light chain of inter-alpha-inhibitor known for its inhibition of the action of many serine proteinases like trypsin and chymotrypsin. It exhibits a strong calcium oxalate crystal nucleation and aggregation inhibitory activity[62]. Immunohistochemical studies have shown that bikunin is localized in proximal tubules and the thin descending segment of the loop of Henle. It is absent in the glomeruli, distal tubules, or collecting ducts[63]. In subjects with lithiasis, bikunin does not prevent crystallization so well as in healthy subjects[64]. In a study by Médétognon-Benissan *et al*[65], strong inhibitory effect of bikunin on CaOx crystallization was confirmed by *in vitro* studies. On the other hand, a comparison of this protein in urine of adults with calcium oxalate lithiasis with urine of healthy subjects by means of the ELISA method, confirmed that bikunin level was 50% lower in affected subjects. On the contrary, a statistically significantly higher excretion of this protein in urine was observed in children with lithiasis [48].

Nephrocalcin

NC was the first urinary protein found to have crystal inhibitory properties[66]. This is a 14-kDa glycoprotein. It is a very potent inhibitor, compared to THP and OPN, the two other inhibitors, and is probably of major importance in protecting the kidneys against urinary supersaturation. NC contains γ-carboxyglutamic acid and has been shown to inhibit crystal growth, nucleation, and aggregation. The absence of γ-carboxyglutamic acid in the NC molecule from stone forming patients reduces its ability to inhibit nucleation and growth of calcium oxalate crystals[66,67].

To date, four isoforms of NC in urine have been reported. NC A and B isoforms are strong inhibitors, and C and D isoforms act as promoters for kidney stones[68].

A fifth NC was identified, called NC-PreA found in patients with renal cell carcinoma and in calcium oxalate renal extractions. In a recent study in children, Noyan *et al*[69] included 41 boys and girls with urinary stones and 25 age- and sex-matched healthy controls. The NC-PreA/creatinine ratio is significantly higher in patients with renal stones than in controls. This finding observed in stone-forming patients indicates that this ratio, too, may also be an important stimulatory molecule for urinary stone disease.

CONCLUSION

Despite many studies that have explored the proteomics of urinary stones, we still do not know the exact role of many of these matrix proteins found in kidney stones in calcium salt crystallization. The invariable presence of proteins in stones matrix raises the possibility that they play a role in stone formation, like the role that proteins have in healthy biomineralization. Are they protective molecules that were overwhelmed by mineral supersaturation? Can mineralization be promoted by these proteins? Are they merely a response to the disease process, including oxidative stress and inflammation? More studies are needed comparing urinary stone proteomics between stone formers and non-stone formers to elucidate the role of stone matrix proteins in stone formation.

FOOTNOTES

Author contributions: Negri AL and Spivacow FR performed article design, literature review, and manuscript writing and final edition; Negri AL and Spivacow FR contributed equally to this work.

Conflict-of-interest statement: Both authors declare no conflict of interest for this article.

Country/Territory of origin: Argentina

ORCID number: Armando Luis Negri 0000-0003-1243-6568; Francisco Rodolfo Spivacow 0000-0001-7048-3317.

S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Ma YJ

REFERENCES

1 **Bihl G**, Meyers A. Recurrent renal stone disease-advances in pathogenesis and clinical management. *Lancet* 2001; **358**: 651-656 [PMID: 11530173 DOI: 10.1016/S0140-6736(01)05782-8]
2 **Khan SR**, Kok DJ. Modulators of urinary stone formation. *Front Biosci* 2004; **9**: 1450-1482 [PMID: 14977559 DOI: 10.2741/1347]
3 **Petrit Nuraj PN**, Agron Beqiri AB. [The pathomorphology of urolithiasis and the chemical analysis of the stones by x-ray diffraction and infrared spectroscopy]. *Urologiia* 2021; 30-34 [PMID: 34967161]
4 **Turudic D**, Batinic D, Golubic AT, Lovric M, Milosevic D. Calcium oxalate urolithiasis in children: urinary promoters/inhibitors and role of their ratios. *Eur J Pediatr* 2016; **175**: 1959-1965 [PMID: 27730307 DOI: 10.1007/s00431-016-2792-9]
5 **Coe FL**, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. *Nat Rev Nephrol* 2016; **12**: 519-533 [PMID: 27452364 DOI: 10.1038/nrneph.2016.101]
6 **Okumura N**, Tsujihata M, Momohara C, Yoshioka I, Suto K, Nonomura N, Okuyama A, Takao T. Diversity in protein

profiles of individual calcium oxalate kidney stones. *PLoS One* 2013; **8**: e68624 [PMID: 23874695 DOI: 10.1371/journal.pone.0068624]
7 **Gill WB**, Karesh JW, Garsin L, Roma MJ. Inhibitory effects of urinary macromolecules on the crystallization of calcium oxalate. *Invest Urol* 1977; **15**: 95-99 [PMID: 903217]
8 **Sheng X**, Ward MD, Wesson JA. Adhesion between molecules and calcium oxalate crystals: critical interactions in kidney stone formation. *J Am Chem Soc* 2003; **125**: 2854-2855 [PMID: 12617634 DOI: 10.1021/ja029575h]
9 **Canales BK**, Anderson L, Higgins L, Ensrud-Bowlin K, Roberts KP, Wu B, Kim IW, Monga M. Proteome of human calcium kidney stones. *Urology* 2010; **76**: 1017.e13-1017.e20 [PMID: 20709378 DOI: 10.1016/j.urology.2010.05.005]
10 **Merchant ML**, Cummins TD, Wilkey DW, Salyer SA, Powell DW, Klein JB, Lederer ED. Proteomic analysis of renal calculi indicates an important role for inflammatory processes in calcium stone formation. *Am J Physiol Renal Physiol* 2008; **295**: F1254-F1258 [PMID: 18701630 DOI: 10.1152/ajprenal.00134.2008]
11 **Kaneko K**, Kobayashi R, Yasuda M, Izumi Y, Yamanobe T, Shimizu T. Comparison of matrix proteins in different types of urinary stone by proteomic analysis using liquid chromatography-tandem mass spectrometry. *Int J Urol* 2012; **19**: 765-772 [PMID: 22494008 DOI: 10.1111/j.1442-2042.2012.03005.x]
12 **Yang Y**, Hong S, Li C, Zhang J, Hu H, Chen X, Jiang K, Sun F, Wang Q, Wang S. Proteomic analysis reveals some common proteins in the kidney stone matrix. *PeerJ* 2021; **9**: e11872 [PMID: 34395096 DOI: 10.7717/peerj.11872]
13 **Wang Q**, Sun Y, Yang Y, Li C, Zhang J, Wang S. Quantitative proteomic analysis of urinary exosomes in kidney stone patients. *Transl Androl Urol* 2020; **9**: 1572-1584 [PMID: 32944520 DOI: 10.21037/tau-20-41]
14 **Kumar S**, Muchmore A. Tamm-Horsfall protein--uromodulin (1950-1990). *Kidney Int* 1990; **37**: 1395-1401 [PMID: 2194064 DOI: 10.1038/ki.1990.128]
15 **Serafini-Cessi F**, Malagolini N, Cavallone D. Tamm-Horsfall glycoprotein: biology and clinical relevance. *Am J Kidney Dis* 2003; **42**: 658-676 [PMID: 14520616 DOI: 10.1016/s0272-6386(03)00829-1]
16 **Garimella PS**, Sarnak MJ. Uromodulin in kidney health and disease. *Curr Opin Nephrol Hypertens* 2017; **26**: 136-142 [PMID: 27898524 DOI: 10.1097/MNH.0000000000000299]
17 **Scolari F**, Caridi G, Rampoldi L, Tardanico R, Izzi C, Pirulli D, Amoroso A, Casari G, Ghiggeri GM. Uromodulin storage diseases: clinical aspects and mechanisms. *Am J Kidney Dis* 2004; **44**: 987-999 [PMID: 15558519 DOI: 10.1053/j.ajkd.2004.08.021]
18 **Bichler KH**, Ideler V, Harzmann R. Uromucoid excretion in normal individuals and stone formers. *Curr Probl Clin Biochem* 1979; 309-324 [PMID: 446078]
19 **Fraser M**, Joyce AD, Thomas DF, Eardley I, Clark PB. Minimally invasive treatment of urinary tract calculi in children. *BJU Int* 1999; **84**: 339-342 [PMID: 10468733 DOI: 10.1046/j.1464-410x.1999.00166.x]
20 **Baggio B**, Gambaro G, Favaro S, Borsatti A, Pavanello L, Siviero B, Zacchello G, Rizzoni GF. Juvenile renal stone disease: a study of urinary promoting and inhibiting factors. *J Urol* 1983; **130**: 1133-1135 [PMID: 6315967 DOI: 10.1016/s0022-5347(17)51721-8]
21 **Jaggi M**, Nakagawa Y, Zipperle L, Hess B. Tamm-Horsfall protein in recurrent calcium kidney stone formers with positive family history: abnormalities in urinary excretion, molecular structure and function. *Urol Res* 2007; **35**: 55-62 [PMID: 17345077 DOI: 10.1007/s00240-007-0083-7]
22 **Glauser A**, Hochreiter W, Jaeger P, Hess B. Determinants of urinary excretion of Tamm-Horsfall protein in non-selected kidney stone formers and healthy subjects. *Nephrol Dial Transplant* 2000; **15**: 1580-1587 [PMID: 11007825 DOI: 10.1093/ndt/15.10.1580]
23 **Argade S**, Chen T, Shaw T, Berecz Z, Shi W, Choudhury B, Parsons CL, Sur RL. An evaluation of Tamm-Horsfall protein glycans in kidney stone formers using novel techniques. *Urolithiasis* 2015; **43**: 303-312 [PMID: 25935139 DOI: 10.1007/s00240-015-0775-3]
24 **Viswanathan P**, Rimer JD, Kolbach AM, Ward MD, Kleinman JG, Wesson JA. Calcium oxalate monohydrate aggregation induced by aggregation of desialylated Tamm-Horsfall protein. *Urol Res* 2011; **39**: 269-282 [PMID: 21229239 DOI: 10.1007/s00240-010-0353-7]
25 **Mo L**, Zhu XH, Huang HY, Shapiro E, Hasty DL, Wu XR. Ablation of the Tamm-Horsfall protein gene increases susceptibility of mice to bladder colonization by type 1-fimbriated Escherichia coli. *Am J Physiol Renal Physiol* 2004; **286**: F795-F802 [PMID: 14665435 DOI: 10.1152/ajprenal.00357.2003]
26 **Wu XR**. Interstitial calcinosis in renal papillae of genetically engineered mouse models: relation to Randall's plaques. *Urolithiasis* 2015; **43** Suppl 1: 65-76 [PMID: 25096800 DOI: 10.1007/s00240-014-0699-3]
27 **Khan SR**. Reactive oxygen species as the molecular modulators of calcium oxalate kidney stone formation: evidence from clinical and experimental investigations. *J Urol* 2013; **189**: 803-811 [PMID: 23022011 DOI: 10.1016/j.juro.2012.05.078]
28 **Khan SR**. Reactive oxygen species, inflammation and calcium oxalate nephrolithiasis. *Transl Androl Urol* 2014; **3**: 256-276 [PMID: 25383321 DOI: 10.3978/j.issn.2223-4683.2014.06.04]
29 **Aihara K**, Byer KJ, Khan SR. Calcium phosphate-induced renal epithelial injury and stone formation: involvement of reactive oxygen species. *Kidney Int* 2003; **64**: 1283-1291 [PMID: 12969146 DOI: 10.1046/j.1523-1755.2003.00226.x]
30 **Umekawa T**, Chegini N, Khan SR. Oxalate ions and calcium oxalate crystals stimulate MCP-1 expression by renal epithelial cells. *Kidney Int* 2002; **61**: 105-112 [PMID: 11786090 DOI: 10.1046/j.1523-1755.2002.00106.x]
31 **LaFavers KA**, Macedo E, Garimella PS, Lima C, Khan S, Myslinski J, McClintick J, Witzmann FA, Winfree S, Phillips CL, Hato T, Dagher PC, Wu XR, El-Achkar TM, Micanovic R. Circulating uromodulin inhibits systemic oxidative stress by inactivating the TRPM2 channel. *Sci Transl Med* 2019; **11** [PMID: 31578243 DOI: 10.1126/scitranslmed.aaw3639]
32 **Foell D**, Wittkowski H, Vogl T, Roth J. S100 proteins expressed in phagocytes: a novel group of damage-associated molecular pattern molecules. *J Leukoc Biol* 2007; **81**: 28-37 [PMID: 16943388 DOI: 10.1189/jlb.0306170]
33 **Wolf R**, Howard OM, Dong HF, Voscopoulos C, Boeshans K, Winston J, Divi R, Gunsior M, Goldsmith P, Ahvazi B, Chavakis T, Oppenheim JJ, Yuspa SH. Chemotactic activity of S100A7 (Psoriasin) is mediated by the receptor for advanced glycation end products and potentiates inflammation with highly homologous but functionally distinct S100A15. *J Immunol* 2008; **181**: 1499-1506 [PMID: 18606705 DOI: 10.4049/jimmunol.181.2.1499]
34 **Foell D**, Wittkowski H, Roth J. Mechanisms of disease: a 'DAMP' view of inflammatory arthritis. *Nat Clin Pract*

Rheumatol 2007; **3**: 382-390 [PMID: 17599072 DOI: 10.1038/ncprheum0531]
35 **Chan JK**, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, Horwood N, Nanchahal J. Alarmins: awaiting a clinical response. *J Clin Invest* 2012; **122**: 2711-2719 [PMID: 22850880 DOI: 10.1172/JCI62423]
36 **Edgeworth J**, Gorman M, Bennett R, Freemont P, Hogg N. Identification of p8,14 as a highly abundant heterodimeric calcium binding protein complex of myeloid cells. *J Biol Chem* 1991; **266**: 7706-7713 [PMID: 2019594]
37 **Averill MM**, Barnhart S, Becker L, Li X, Heinecke JW, Leboeuf RC, Hamerman JA, Sorg C, Kerkhoff C, Bornfeldt KE. S100A9 differentially modifies phenotypic states of neutrophils, macrophages, and dendritic cells: implications for atherosclerosis and adipose tissue inflammation. *Circulation* 2011; **123**: 1216-1226 [PMID: 21382888 DOI: 10.1161/CIRCULATIONAHA.110.985523]
38 **Vogl T**, Ludwig S, Goebeler M, Strey A, Thorey IS, Reichelt R, Foell D, Gerke V, Manitz MP, Nacken W, Werner S, Sorg C, Roth J. MRP8 and MRP14 control microtubule reorganization during transendothelial migration of phagocytes. *Blood* 2004; **104**: 4260-4268 [PMID: 15331440 DOI: 10.1182/blood-2004-02-0446]
39 **Vogl T**, Tenbrock K, Ludwig S, Leukert N, Ehrhardt C, van Zoelen MA, Nacken W, Foell D, van der Poll T, Sorg C, Roth J. Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat Med* 2007; **13**: 1042-1049 [PMID: 17767165 DOI: 10.1038/nm1638]
40 **Harja E**, Bu DX, Hudson BI, Chang JS, Shen X, Hallam K, Kalea AZ, Lu Y, Rosario RH, Oruganti S, Nikolla Z, Belov D, Lalla E, Ramasamy R, Yan SF, Schmidt AM. Vascular and inflammatory stresses mediate atherosclerosis *via* RAGE and its ligands in apoE-/- mice. *J Clin Invest* 2008; **118**: 183-194 [PMID: 18079965 DOI: 10.1172/jci32703]
41 **Loser K**, Vogl T, Voskort M, Lueken A, Kupas V, Nacken W, Klenner L, Kuhn A, Foell D, Sorokin L, Luger TA, Roth J, Beissert S. The Toll-like receptor 4 ligands Mrp8 and Mrp14 are crucial in the development of autoreactive CD8+ T cells. *Nat Med* 2010; **16**: 713-717 [PMID: 20473308 DOI: 10.1038/nm.2150]
42 **Riva M**, Källberg E, Björk P, Hancz D, Vogl T, Roth J, Ivars F, Leanderson T. Induction of nuclear factor-κB responses by the S100A9 protein is Toll-like receptor-4-dependent. *Immunology* 2012; **137**: 172-182 [PMID: 22804476 DOI: 10.1111/j.1365-2567.2012.03619.x]
43 **Holzinger D**, Frosch M, Kastrup A, Prince FH, Otten MH, Van Suijlekom-Smit LW, ten Cate R, Hoppenreijs EP, Hansmann S, Moncrieffe H, Ursu S, Wedderburn LR, Roth J, Foell D, Wittkowski H. The Toll-like receptor 4 agonist MRP8/14 protein complex is a sensitive indicator for disease activity and predicts relapses in systemic-onset juvenile idiopathic arthritis. *Ann Rheum Dis* 2012; **71**: 974-980 [PMID: 22267331 DOI: 10.1136/annrheumdis-2011-200598]
44 **Källberg E**, Vogl T, Liberg D, Olsson A, Björk P, Wikström P, Bergh A, Roth J, Ivars F, Leanderson T. S100A9 interaction with TLR4 promotes tumor growth. *PLoS One* 2012; **7**: e34207 [PMID: 22470535 DOI: 10.1371/journal.pone.0034207]
45 **Yonekawa K**, Neidhart M, Altwegg LA, Wyss CA, Corti R, Vogl T, Grigorian M, Gay S, Lüscher TF, Maier W. Myeloid related proteins activate Toll-like receptor 4 in human acute coronary syndromes. *Atherosclerosis* 2011; **218**: 486-492 [PMID: 21782178 DOI: 10.1016/j.atherosclerosis.2011.06.020]
46 **Momohara C**, Tsujihata M, Yoshioka I, Tsujimura A, Nonomura N, Okuyama A. Mechanism underlying the low prevalence of pediatric calcium oxalate urolithiasis. *J Urol* 2009; **182**: 1201-1209 [PMID: 19625038 DOI: 10.1016/j.juro.2009.05.007]
47 **Mushtaq S**, Siddiqui AA, Naqvi ZA, Rattani A, Talati J, Palmberg C, Shafqat J. Identification of myeloperoxidase, alpha-defensin and calgranulin in calcium oxalate renal stones. *Clin Chim Acta* 2007; **384**: 41-47 [PMID: 17610860 DOI: 10.1016/j.cca.2007.05.015]
48 **Bergsland KJ**, Kelly JK, Coe BJ, Coe FL. Urine protein markers distinguish stone-forming from non-stone-forming relatives of calcium stone formers. *Am J Physiol Renal Physiol* 2006; **291**: F530-F536 [PMID: 16622176 DOI: 10.1152/ajprenal.00370.2005]
49 **Jobs K**, Jung A, Lewicki S, Murawski P, Pączek L, Zdanowski R. Assessment of Cross-correlations Between Selected Macromolecules in Urine of Children with Idiopathic Hypercalciuria. *Urol J* 2018; **15**: 231-237 [PMID: 29353465 DOI: 10.22037/uj.v0i0.3956]
50 **Icer MA**, Gezmen-Karadag M. The multiple functions and mechanisms of osteopontin. *Clin Biochem* 2018; **59**: 17-24 [PMID: 30003880 DOI: 10.1016/j.clinbiochem.2018.07.003]
51 **Clemente N**, Raineri D, Cappellano G, Boggio E, Favero F, Soluri MF, Dianzani C, Comi C, Dianzani U, Chiocchetti A. Osteopontin Bridging Innate and Adaptive Immunity in Autoimmune Diseases. *J Immunol Res* 2016; **2016**: 7675437 [PMID: 28097158 DOI: 10.1155/2016/7675437]
52 **Fisher LW**, Torchia DA, Fohr B, Young MF, Fedarko NS. Flexible structures of SIBLING proteins, bone sialoprotein, and osteopontin. *Biochem Biophys Res Commun* 2001; **280**: 460-465 [PMID: 11162539 DOI: 10.1006/bbrc.2000.4146]
53 **Kazanecki CC**, Uzwiak DJ, Denhardt DT. Control of osteopontin signaling and function by post-translational phosphorylation and protein folding. *J Cell Biochem* 2007; **102**: 912-924 [PMID: 17910028 DOI: 10.1002/jcb.21558]
54 **Kiefer FW**, Zeyda M, Todoric J, Huber J, Geyeregger R, Weichhart T, Aszmann O, Ludvik B, Silberhumer GR, Prager G, Stulnig TM. Osteopontin expression in human and murine obesity: extensive local up-regulation in adipose tissue but minimal systemic alterations. *Endocrinology* 2008; **149**: 1350-1357 [PMID: 18048491 DOI: 10.1210/en.2007-1312]
55 **Kohri K**, Nomura S, Kitamura Y, Nagata T, Yoshioka K, Iguchi M, Yamate T, Umekawa T, Suzuki Y, Sinohara H. Structure and expression of the mRNA encoding urinary stone protein (osteopontin). *J Biol Chem* 1993; **268**: 15180-15184 [PMID: 8325891]
56 **Konya E**, Umekawa T, Iguchi M, Kurita T. The role of osteopontin on calcium oxalate crystal formation. *Eur Urol* 2003; **43**: 564-571 [PMID: 12706004 DOI: 10.1016/s0302-2838(03)00088-5]
57 **Khan SR**, Johnson JM, Peck AB, Cornelius JG, Glenton PA. Expression of osteopontin in rat kidneys: induction during ethylene glycol induced calcium oxalate nephrolithiasis. *J Urol* 2002; **168**: 1173-1181 [PMID: 12187263 DOI: 10.1016/S0022-5347(05)64621-6]
58 **Kleinman JG**, Wesson JA, Hughes J. Osteopontin and calcium stone formation. *Nephron Physiol* 2004; **98**: p43-p47 [PMID: 15499214 DOI: 10.1159/000080263]
59 **Tsuji H**, Shimizu N, Nozawa M, Umekawa T, Yoshimura K, De Velasco MA, Uemura H, Khan SR. Osteopontin

knockdown in the kidneys of hyperoxaluric rats leads to reduction in renal calcium oxalate crystal deposition. *Urolithiasis* 2014; **42**: 195-202 [PMID: 24619192 DOI: 10.1007/s00240-014-0649-0]

60 **Safarinejad MR**, Shafiei N, Safarinejad S. Association between polymorphisms in osteopontin gene (SPP1) and first episode calcium oxalate urolithiasis. *Urolithiasis* 2013; **41**: 303-313 [PMID: 23784265 DOI: 10.1007/s00240-013-0582-7]

61 **Xiao X**, Dong Z, Ye X, Yan Y, Chen X, Pan Q, Xie Y, Xie J, Wang Q, Yuan Q. Association between OPN genetic variations and nephrolithiasis risk. *Biomed Rep* 2016; **5**: 321-326 [PMID: 27602211 DOI: 10.3892/br.2016.724]

62 **Atmani F**, Khan SR. Role of urinary bikunin in the inhibition of calcium oxalate crystallization. *J Am Soc Nephrol* 1999; **10** Suppl 14: S385-S388 [PMID: 10541269]

63 **Okuyama M**, Yamaguchi S, Yachiku S. Identification of bikunin isolated from human urine inhibits calcium oxalate crystal growth and its localization in the kidneys. *Int J Urol* 2003; **10**: 530-535 [PMID: 14516400 DOI: 10.1046/j.1442-2042.2003.00677.x]

64 **De Yoreo JJ**, Qiu SR, Hoyer JR. Molecular modulation of calcium oxalate crystallization. *Am J Physiol Renal Physiol* 2006; **291**: F1123-F1131 [PMID: 17082348 DOI: 10.1152/ajprenal.00136.2006]

65 **Médétognon-Benissan J**, Tardivel S, Hennequin C, Daudon M, Drüeke T, Lacour B. Inhibitory effect of bikunin on calcium oxalate crystallization in vitro and urinary bikunin decrease in renal stone formers. *Urol Res* 1999; **27**: 69-75 [PMID: 10092156 DOI: 10.1007/s002400050091]

66 **Asplin J**, DeGanello S, Nakagawa YN, Coe FL. Evidence that nephrocalcin and urine inhibit nucleation of calcium oxalate monohydrate crystals. *Am J Physiol* 1991; **261**: F824-F830 [PMID: 1951713 DOI: 10.1152/ajprenal.1991.261.5.F824]

67 **Nakagawa Y**, Ahmed M, Hall SL, Deganello S, Coe FL. Isolation from human calcium oxalate renal stones of nephrocalcin, a glycoprotein inhibitor of calcium oxalate crystal growth. Evidence that nephrocalcin from patients with calcium oxalate nephrolithiasis is deficient in gamma-carboxyglutamic acid. *J Clin Invest* 1987; **79**: 1782-1787 [PMID: 3584470 DOI: 10.1172/JCI113019]

68 **Nakagawa Y**, Parks JH, Kézdy FJ, Coe FL. Molecular abnormality of urinary glycoprotein crystal growth inhibitor in calcium nephrolithiasis. *Trans Assoc Am Physicians* 1985; **98**: 281-289 [PMID: 3842199]

69 **Noyan A**, Yaşar H, Bayazit AK, Anarat R, Bayazit Y, Anarat A. Urinary nephrocalcin excretion in children with urolithiasis. *Nephron Physiol* 2003; **94**: p59-p61 [PMID: 12972707 DOI: 10.1159/000072518]

World Journal of Nephrology

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

World J Nephrol 2023 March 25; 12(2): 29-39

DOI: 10.5527/wjn.v12.i2.29

ISSN 2220-6124 (online)

MINIREVIEWS

Point of care ultrasonography in onco-nephrology: A stride toward better physical examination

Bhavna Bhasin-Chhabra, Abhilash Koratala

Specialty type: Critical care medicine

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): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Munasinghe B, Sri Lanka; Vlachopanos G, Greece

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 20, 2023
Revised: January 27, 2023
Accepted: March 9, 2023
Article in press: March 9, 2023
Published online: March 25, 2023

Bhavna Bhasin-Chhabra, Division of Nephrology and Hypertension, Mayo Clinic, Scottsdale, AZ 85259, United States

Abhilash Koratala, Division of Nephrology, Medical College of Wisconsin, Milwaukee, WI 53226, United States

Corresponding author: Abhilash Koratala, MD, Associate Professor, Division of Nephrology, Medical College of Wisconsin, 8701 W Watertown Plank Rd, 7th floor, Milwaukee, WI 53226, United States. akoratala@mcw.edu

Abstract

Onco-Nephrology is an emerging subspecialty of Nephrology that focuses on a broad spectrum of renal disorders that can arise in patients with cancer. It encompasses acute kidney injury (AKI), complex fluid, electrolyte, and acid-base disorders, as well as chronic kidney disease caused or exacerbated by cancer and/or its treatment. In many such scenarios including AKI and hyponatremia, objective evaluation of hemodynamics is vital for appropriate management. Point of care ultrasonography (POCUS) is a limited ultrasound exam performed at the bedside and interpreted by the treating physician intended to answer focused clinical questions and guide therapy. Compared to conventional physical examination, POCUS offers substantially higher diagnostic accuracy for various structural and hemodynamic derangements. In this narrative review, we provide an overview of the utility of POCUS enhanced physical examination for the Onconephrologist supported by the current evidence and our experience-based opinion.

Key Words: Point of care ultrasonography; Onco-nephrology; Acute kidney injury; Hyponatremia; Volume assessment

Core Tip: Point of care ultrasonography is a valuable adjunct to physical examination in patients with cancer and renal dysfunction or fluid/electrolyte disorders. It provides better diagnostic accuracy than conventional physical examination. Proper training is the key to effectively integrate this diagnostic tool into routine clinical practice.

Citation: Bhasin-Chhabra B, Koratala A. Point of care ultrasonography in onco-nephrology: A stride toward better physical examination. *World J Nephrol* 2023; 12(2): 29-39
URL: https://www.wjgnet.com/2220-6124/full/v12/i2/29.htm
DOI: https://dx.doi.org/10.5527/wjn.v12.i2.29

INTRODUCTION

Point of care ultrasonography (POCUS) is a focused ultrasound examination performed by the clinician at the bedside to guide patient management[1]. Recent years have witnessed a swift uptake of POCUS in almost all the clinical specialties and several medical schools have started teaching this skill to their students. According to a 2020 survey, 57% of the responding United States medical schools (69 out of 122) integrated POCUS instruction into undergraduate medical curriculum[2]. Once confined to procedural guidance such as dialysis catheter placement, the scope of POCUS in nephrology has now greatly expanded to include a wide array of diagnostic applications ranging from kidney ultrasound to focused echocardiography[3,4]. Some nephrology fellowship programs have even incorporated detailed hemodynamic monitoring using advanced Doppler techniques into their curricula[5]. Figure 1 illustrates the sonographic applications that can be performed by nephrologists trained in POCUS. We have also seen in these past few years the emergence of Onco-Nephrology as a subspecialty within Nephrology[6,7]. This field focuses on management of kidney disorders in patients who have an active malignancy and are undergoing treatment for this. The breadth of kidney disorders seen and addressed in Onco-Nephrology practice includes acute kidney injury, hypertension, proteinuria, chronic kidney disease, fluid and electrolyte disorders to name a few. This article seeks to discuss the role and potential of POCUS in positively impacting the clinical practice of Onco-Nephrology by providing a few representative clinical scenarios.

THE RATIONALE FOR POCUS ENHANCED PHYSICAL EXAMINATION

Unlike a consultative ultrasound study which is expected to image an entire area in question (*e.g.*, abdominal ultrasound) with documentation of predefined measurements and parameters, POCUS is intended to answer focused questions that either narrow the differential diagnosis or provide a final diagnosis when interpreted in conjunction with history and physical examination by the treating physician. Moreover, it allows monitoring of a particular parameter in response to therapy without having to repeat the whole comprehensive study. For example, a nephrologist can follow a patient with uremic pericardial effusion in the outpatient dialysis unit with serial POCUS exams thereby avoiding repeated trips of the patient to the echocardiography laboratory. It is analogous to using a stethoscope (*point of care* device) to listen to heart and lung sounds, which is why some authors describe POCUS as a fifth pillar of bedside physical examination in addition to inspection, palpation, percussion, and auscultation[8]. This raises the question why we need an enhancement to physical examination in the first place and does POCUS have better diagnostic accuracy. The diagnostic performance of conventional physical examination is poor for several clinical questions that nephrologists deal with in day-to-day practice. For example, in a study including 50 patients with severely reduced left ventricular ejection fraction, the combined sensitivity of rales, edema, and elevated jugular venous pressure (JVP) was only 58% to detect an elevated pulmonary capillary wedge pressure of > 22 mmHg[9]. Similarly, in another study including 58 non-edematous patients with serum sodium less than 130 mEq/L, clinical assessment was able to accurately identify only 47% of hypovolemic and 48% of euvolemic patients[10]. Likewise, in a meta-analysis of 22 studies, pooled sensitivities of orthopnea, peripheral edema, JVP, third heart sound and rales were only 50%, 51%, 39%, 13% and 60% respectively to diagnose congestive heart failure[11]. Further, there is no conventional physical examination parameter to answer focused questions requiring visualization of internal anatomy such as the presence or absence of hydronephrosis, systemic venous congestion *etc.* POCUS aids in answering such questions at the bedside without having to wait for multiple consultative ultrasound studies and potentially avoiding unnecessary radiation. The diagnostic superiority of POCUS is well established in various clinical settings compared to conventional examination. For instance, in a study including 79 patients on hemodialysis, the sensitivity of lung crackles and peripheral edema was only 9% and 3% respectively to detect severe lung congestion found on lung POCUS[12]. In the context of critical illness, a study including 926 patients admitted to the intensive care unit found that 51% of those who had pulmonary edema on lung POCUS demonstrated normal auscultatory findings[13]. With respect to focused cardiac ultrasound, in a recent meta-analysis of 9 studies, the sensitivity of POCUS-assisted examination for diagnosing left ventricular dysfunction and valvular disease was found to be significantly higher compared to conventional assessment (84% *vs* 43%, and 71% *vs* 46% respectively)[14]. In addition, the utility of POCUS for rapid evaluation and management of patients with undifferentiated hypotension,

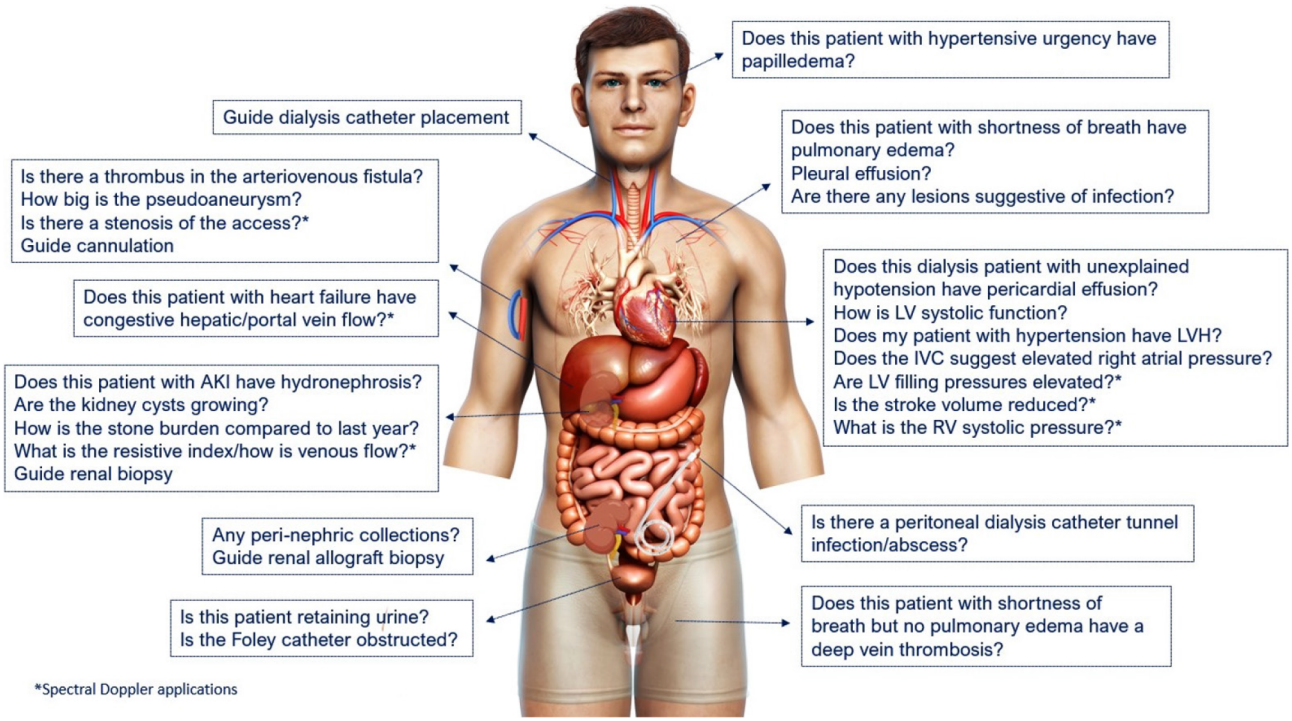


Figure 1 Scope of nephrology-related point of care ultrasonography. Organ-specific focused questions that can be answered by bedside ultrasonography. Those marked with asterisk (*) indicate advanced sonographic applications requiring a higher operator skill level/additional training. Figure reused from reference # 3 with kind permission of the American Society of Nephrology.

chest trauma and possible pericardial tamponade is well-recognized[15]. All these studies highlight the need for enhancing our bedside examination with POCUS. Furthermore, there are emerging data suggesting that POCUS enhances patient satisfaction and shared diagnostic understanding between patients and clinicians[16,17]. Even in developing countries and low-resource settings where one might expect slow adoption of technological advances due to cost issues, POCUS has shown to favorably impact clinical care. In fact, POCUS might be more beneficial in these scenarios to facilitate timely and accurate diagnosis as patients often present with advanced disease. For example, in a Tanzanian cohort of 55 hospitalized patients, a change in management plan was supported by POCUS findings in 53% cases leading to earlier initiation of appropriate treatment[18]. Similar findings were observed in a study from Sri Lanka where POCUS utilization in critically ill patients facilitated early diagnosis and/or interventions[19].

Below are a few situations commonly encountered in Onco-Nephrology practice where POCUS enhanced physical examination can provide valuable information.

CLINICAL SCENARIO 1: ACUTE KIDNEY INJURY IN CANCER

Acute kidney injury (AKI) is a frequent complication of either the underlying malignancy or its treatment and is an independent predictor of mortality in patients with cancer[20,21]. The incidence of AKI in a large Danish cohort of cancer patients was reported to be 17.5% at 1 year and 27% over the course of 5 years, which highlights the enormity of the problem[22]. Similarly, in a Chinese study, the incidence of AKI in hospitalized cancer patients was reported to be 7.5% (hospital acquired in 6% of the cases)[23]. The etiologies of AKI vary across solid organ and hematological malignancies as well as in patients undergoing stem cell transplantation. Hemodynamic AKI resulting from volume depletion is the predominant cause of AKI in patients with an underlying cancer[24] as they may develop nausea, vomiting or diarrhea as complication of cancer chemotherapy or due to the underlying cancer. Post renal obstructive etiology may be the driver of AKI in patients with genitourinary malignancies or locally invasive primary gynecological or gastrointestinal malignancies or metastatic disease[25]. Moreover, as a significant proportion of malignancies treated with radiotherapy are in the abdomen and pelvis, complications such as radiation-induced ureteral and urethral stenosis must be considered in the differential diagnosis of obstructive nephropathy in these patients[26]. Intrinsic renal injury may be mediated by nephrotoxic chemotherapy, paraproteins, glomerulopathies, contrast exposure, infiltration by the primary malignancy or progression of ischemic kidney injury[25].

POCUS considerations

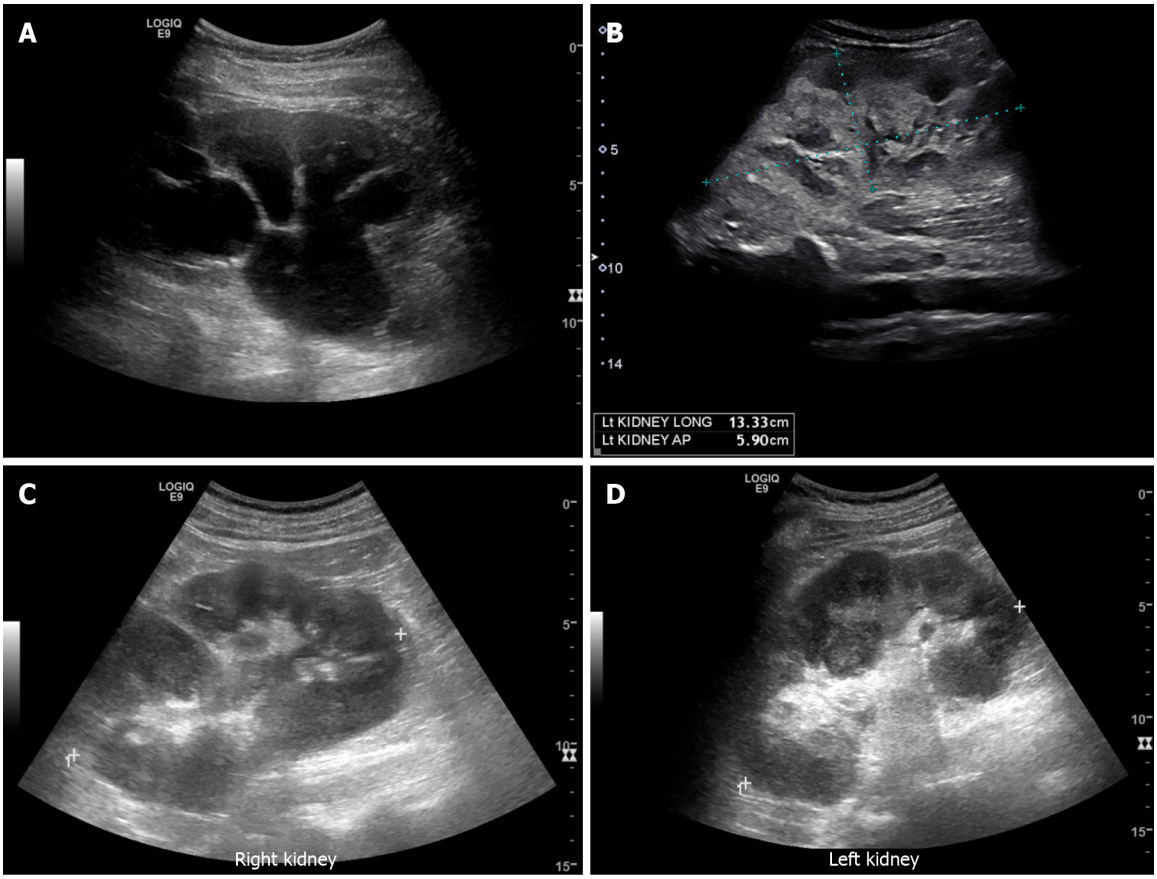
Renal sonography is frequently ordered as part of the initial diagnostic algorithm to rule out obstructive etiology, which is potentially reversible if treated promptly. Bedside POCUS can easily identify hydronephrosis and bladder masses that may be causing urinary obstruction[27]. POCUS can also help delineate intrinsic processes such as infiltrative diseases which may be arising secondary to lymphoma for instance[28]. The kidney size tends to be preserved or larger than expected in these cases with alterations noted in cortical echogenicity. Determination of kidney size and cortical echogenicity while keeping in context the clinical picture can help understand if the renal impairment appears to be a chronic vs. acute process and the realistic probability of renal recovery which can then impact the future diagnostic and therapeutic considerations for these patients[29]. We previously proposed *SECONDS checklist* for systematic interpretation of renal POCUS, which is helpful for novice users[30]. It stands for Size (renal length and thickness), Echogenicity (cortical brightness), Collecting system (obstruction), Outline (smooth *vs* irregular), Notable lesions (such as cysts and stones), Doppler (to distinguish between hydronephrosis and vasculature) and Surroundings (peri-nephric collections). Figure 2 illustrates some of the pathologies seen on renal ultrasound in cancer patients. It is also important to evaluate urinary bladder by POCUS in any patient with AKI and/or oliguria to exclude etiologies such as obstructed Foley catheter or bladder outlet obstruction due to extrinsic compression. Moreover, automated bladder scanners cannot distinguish between pelvic ascites and urinary bladder, which may cause confusion in some cases where POCUS aids in correct diagnosis[31]. As hemodynamic AKI is the most frequent etiology of AKI in patients with cancer, the role of POCUS in this clinical scenario deserves a special mention and is discussed in more detail under volume management below.

CLINICAL SCENARIO 2: VOLUME ASSESSMENT AND MANAGEMENT

Patients with a diagnosis of cancer are often administered intravenous fluids around chemotherapy with the hope of mitigating the risk of AKI, which can lead to iatrogenic fluid overload if the volume status is not objectively assessed. Further, the volume status in these patients is often tenuous, complicated by increased losses through vomiting and diarrhea as well as third spacing due to hypoalbuminemia. Additionally, certain types of chemotherapies may cause cardiac dysfunction predisposing to volume overload. An important reason for Onco-Nephrology consultation on the inpatient Nephrology service is volume assessment and management in patients undergoing stem cell transplantation (SCT) where volume overload occurs frequently. Allogeneic SCT is a well-established treatment for various hematological malignancies as well as a few nonmalignant disorders[32]. Fluid overload in these patients significantly impacts mortality and is associated with poorer survival[33]. As such, it is imperative that we use objective bedside tools such as POCUS to assess hemodynamic status and guide therapy.

POCUS considerations

Multiorgan POCUS in these cases allows accurate volume assessment. We call this the *Pump, Pipes and Leaks* approach. The pump denotes focused cardiac ultrasound, pipes represent inferior vena cava (IVC) ultrasound and systemic venous Doppler, and the leaks indicate assessment of the extravascular lung and abdominal fluid[29] (Figure 3). This way, the whole hemodynamic circuit is assessed instead of relying on isolated parameters such as lung or IVC ultrasound, which are error prone. For example, B-lines on lung ultrasound (vertical artifacts signifying interlobular septal thickening) can be seen in cardiogenic pulmonary edema or an infectious process or even fibrosis. In addition to paying attention to parameters such as irregular pleural line suggestive of local pathology, assessment of left ventricular diastolic function using Doppler aids in proper diagnosis. Similarly, IVC is not reliable to assess right atrial pressure in mechanically ventilated patients. Moreover, it can be chronically dilated in patients with pulmonary hypertension and may not provide meaningful information when interpreted in isolation with respect to guiding therapy. Doppler assessment of systemic venous congestion (VExUS) aids in the management of such patients[34-36]. Detailed discussion of VExUS grading to quantify systemic venous congestion is beyond the scope of this manuscript and is concisely illustrated in Figure 4. On the other hand, IVC can be small despite elevated right atrial pressure in intra-abdominal hypertension. Furthermore, a small collapsible IVC can be seen both in euvolemia and hypovolemia and cannot be used in isolation to distinguish between these two conditions. Bedside assessment of stroke volume helps in this situation as it is expected to be low in hypovolemia. Therefore, a multiparametric POCUS approach is the key to appropriate diagnosis and management of volume disorders and these findings must be interpreted in the right clinical context. As most of this information can be obtained by consultative imaging, some might question the need for clinician-performed POCUS. There are two important justifications for this: (1) Hemodynamics are dynamic. For example, a patient with a normal echocardiogram few days ago might have a completely different hemodynamic picture now. Moreover, it is not prudent to obtain a formal echocardiogram daily to monitor selected hemodynamic parameters in response to treatment when POCUS can accomplish the same during daily rounds; and (2) POCUS reduces fragmentation of care. For instance, to assess the pump, pipes and leaks, multiple consultative



DOI: 10.5527/wjn.v12.i2.29 **Copyright** ©The Author(s) 2023.

Figure 2 Renal ultrasound images demonstrating. A: Severe hydronephrosis (branching anechoic area); B: Enlarged kidney with hyperechoic cortex in a patient with myeloma; C and D: Bilateral renal involvement with lymphoma. Note irregular outline and heterogenous parenchyma.

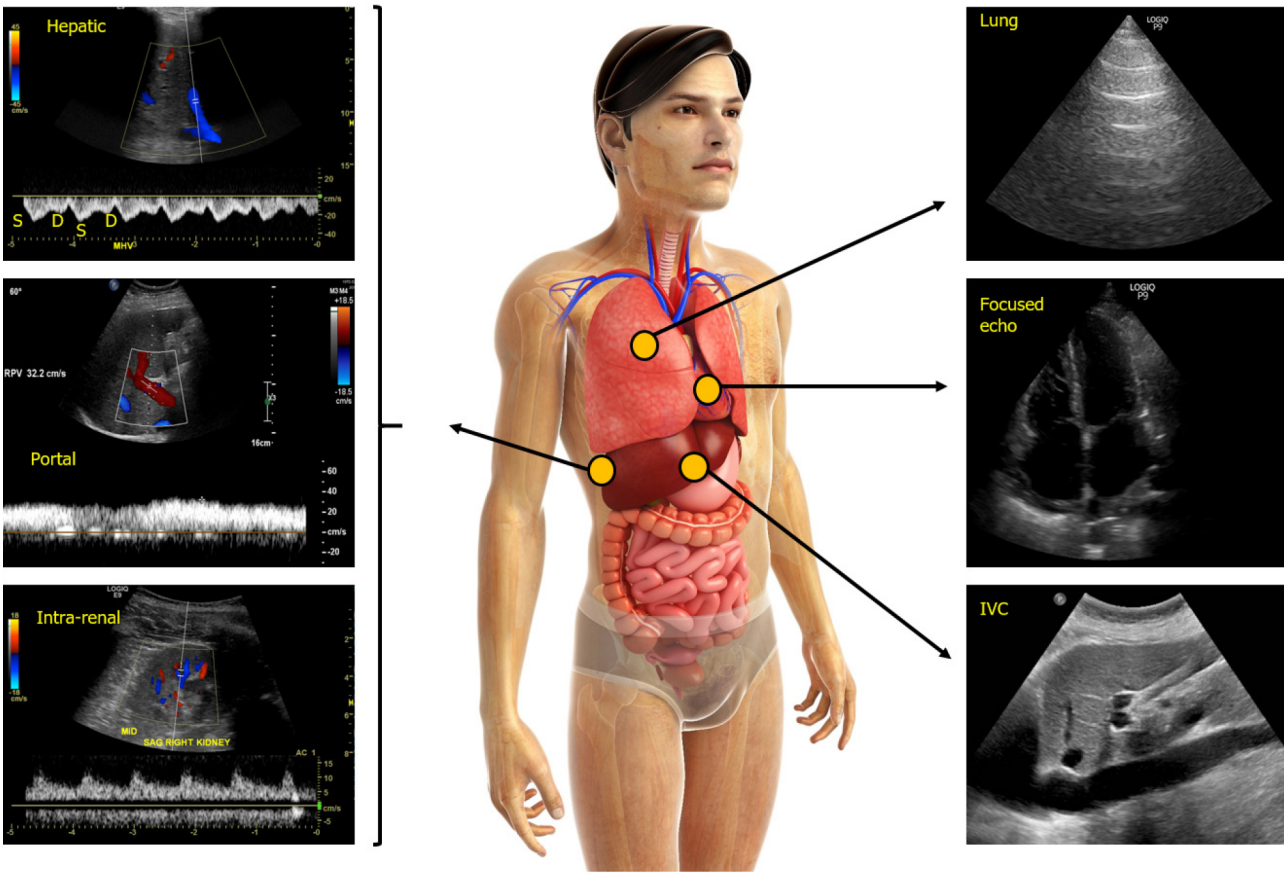
studies must be obtained – echocardiography performed by the cardiology department, a chest radiograph (lung ultrasound is typically not performed by the ultrasound department), an abdominal sonogram (to look for ascites), a right upper quadrant Doppler (for hepatic and portal vein Doppler [a part of VExUS]) and a Doppler renal ultrasound (for renal venous congestion). Conversely, a POCUS-trained physician with knowledge of the patient's clinical history/course can perform a focused assessment answering all the key questions in less than 15 min and tailor therapy accordingly.

CLINICAL SCENARIO 3: EFFUSIONS

Pleural effusion secondary to an underlying malignancy is seen in about 15% of cancers. Metastatic lung (in males) and breast cancer (in females) account for 50%-65% of all cases of malignant pleural effusion. Patients presenting with pleural effusion will require additional imaging for diagnosis and planning of therapeutic interventions. Bedside POCUS is increasingly being utilized for guidance for thoracentesis [37]. Pericardial effusions are noted in 5%-20% patients with an underlying malignancy and significantly impacts the survival and prognosis in these cases[38,39]. Pericardial involvement may result from direct extension of the tumor into the pericardial cavity or hematogenous spread. Opportunistic infections in patients undergoing cancer chemotherapy as well as deranged liver, kidney or cardiac function arising as a result of the underlying cancer or cancer chemotherapy and radiation (like anthracyclines, docetaxel, busulfan, tyrosine kinase inhibitors, arsenic trioxide which can affect the myocardium) may play a role as well in causing pericardial effusion. Majority of the pericardial effusions associated with malignancies are moderate to large in size with pericardial tamponade being noted in one third of the patients with malignant pericardial effusion with poorer outcomes reported in these patients[39]. In addition, ascites is a frequent accompaniment of gastrointestinal and metastatic malignancy.

POCUS considerations

The diagnostic superiority of POCUS to detect multiple effusions is well-established. For example, lung POCUS is more sensitive than physical examination or chest radiography for the detection of small



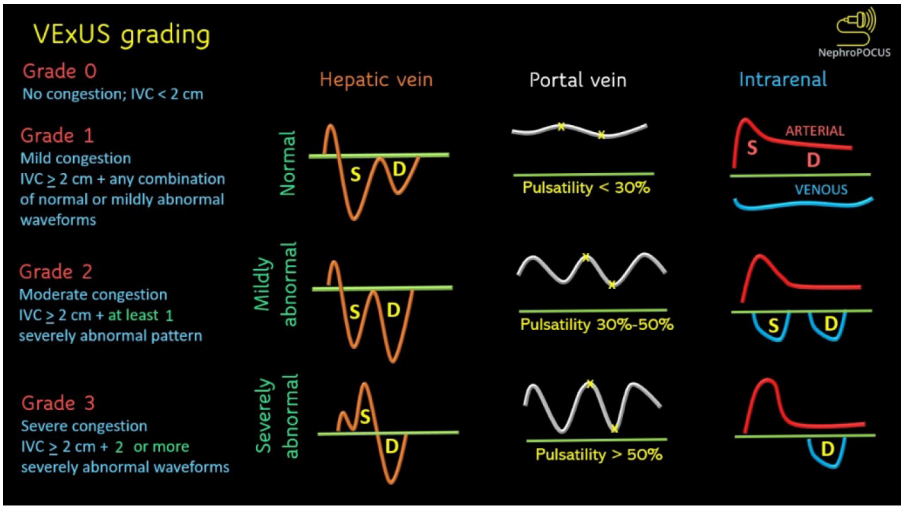
DOI: 10.5527/wjn.v12.i2.29 **Copyright** ©The Author(s) 2023.

Figure 3 Figure illustrating the integration of multi-point sonographic assessment including focused cardiac, lung and venous Doppler ultrasound. Normal waveforms are shown. IVC: Inferior vena cava. Adapted from corresponding author's prior open access publication.

pleural effusions and can detect as small as 3-5 cc of fluid in the pleural space[40-42]. In addition to visualization of pleural effusion, POCUS can help identify loculations in the fluid, thickening and nodularity of the diaphragm, findings which are relatively specific for the diagnosis of malignant pleural effusion. Ultrasound guided pleural biopsies may also be undertaken. The diagnostic accuracy of ultrasound is comparable to computed tomography (CT) in these cases while avoiding the radiation exposure associated with CT imaging. POCUS has also shown to be highly accurate for detecting pericardial effusions of any size and can detect tamponade physiology prior to that of physical examination or vital signs[43]. Therefore, POCUS-performing physician can seek timely consultations prior to clinical decompensation of the patient. Of note, the classic Beck classic triad (jugular venous distension, hypotension, and muffled heart sounds) is a late finding and is neither sensitive nor specific for tamponade[44,45]. With regard to ascites, ultrasound is substantially better than physical examination and can detect as little as 100 cc of peritoneal fluid. In an interesting study from 1982 comparing the diagnostic accuracy of physical examination with that of ultrasound for ascites, overall accuracy of physical examination maneuvers was only 58%[46]. POCUS guidance for paracentesis is essentially a standard procedure in developed countries and has shown to be associated with lower rates of bleeding, decreased hospital length of stay, and cost savings compared to the traditional landmark-based technique[47]. Recently, Nauka *et al*[48] have proposed a FASC protocol (Focused Assessment with Sonography in Cancer), a simple six-point assessment technique to assess multiple effusions in cancer patients that can be easily used by physicians with limited training. Figure 5 illustrates the sonographic appearance of various effusions.

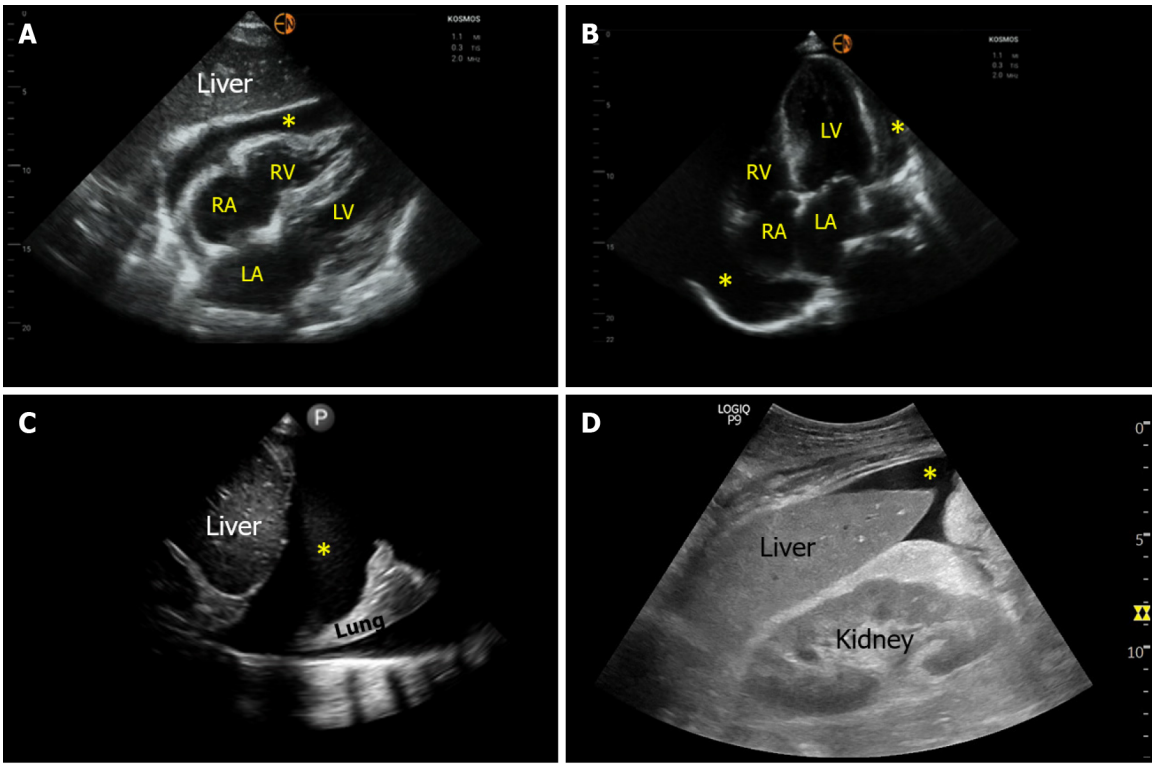
CLINICAL SCENARIO 4: HYPONATREMIA

Hyponatremia is a very common electrolyte abnormality and may be noted in up to 50% of cancer patients[49]. It negatively impacts prognosis in these patients and may be reflective of advanced underlying disease, chemotherapy toxicity and new or progressive liver or cardiac involvement[50]. Syndrome of inappropriate antidiuresis and volume depletion are the most common etiologies for hyponatremia that complicates an underlying malignancy[50,51]. The traditional diagnostic workup for



DOI: 10.5527/wjn.v12.i2.29 **Copyright** ©The Author(s) 2023.

Figure 4 Venous excess ultrasound grading. 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. Adapted from NephroPOCUS.com with permission.



DOI: 10.5527/wjn.v12.i2.29 **Copyright** ©The Author(s) 2023.

Figure 5 Sonographic images demonstrating various effusions. A and B: Pericardial effusion (*) as seen on subxiphoid and apical 4-chamber cardiac views respectively; C: Right pleural effusion (*) seen from the lateral scanning window; D: Ascites (*) seen from the right upper quadrant. RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

hyponatremia begins with measurement of plasma and urine osmolality, urine sodium concentration and assessment of volume status[52]. Unfortunately, physical examination has been reported to have poor sensitivity and specificity in this setting, underscoring the void in our bedside assessment[10].

POCUS considerations

A bedside focused ultrasound examination using proven diagnostic parameters can provide objective assessment of volume status, which would make a case for its incorporation in the initial diagnostic algorithm of hyponatremia[53]. The Pump, Pipes and Leaks approach mentioned above works well in this setting. For example, a small collapsing IVC with low stroke volume suggests hypovolemia whereas the same IVC with normal stroke volume suggests euvolemia. A plethoric IVC is more in favor of hypervolemia though Doppler parameters such as VExUS and transvalvular flow assessment are needed in patients with chronically dilated IVC. Several case reports have been published thus far demonstrating the utility of POCUS in the evaluation and management of hyponatremia as we furnished in our prior publication[53].

SUMMARY AND FUTURE DIRECTIONS

Current evidence clearly indicates that POCUS is superior to that of conventional physical examination in terms of diagnostic accuracy and thereby enhances physicians' confidence in clinical decision making. Future studies must aim to investigate how to better integrate this diagnostic tool in day-to-day Onco-nephrology practice to positively impact measurable outcomes. While one cannot expect mortality benefit just by incorporating a diagnostic modality, outcomes such as duration of hospitalization, time to appropriate diagnosis and treatment, effective decongestion at hospital discharge, recovery of hemodynamic AKI, improvement in patient-reported quality of life, patient and family members' understanding of the diagnosis are all important practical outcomes that POCUS can impact. On a note of caution, POCUS is operator dependent like anything else in medicine (history taking, physical examination, communication with patients) and proper training is the key to avoid unintentional patient harm. With the availability of low-cost ultraportable ultrasound equipment, POCUS is being increasingly utilized by physicians with limited or no training. It is particularly problematic when the user overestimates their skills and/or capabilities of the equipment (*e.g.*, a novice user with limited understanding of Doppler principles assesses stroke volume using suboptimal image obtained by a low-quality handheld ultrasound device resulting in false conclusions and subsequent patient mismanagement). The burden of regulating and overseeing its use falls on the individual institutions till there are uniform guidelines put forth by professional societies for POCUS training and competency assessment. As a matter of fact, Emergency Care Research Institute has listed the increased adoption of POCUS outpacing institutional safeguards as one of the top health technology hazards[54]. One cannot expect to master physical examination by attending a half- or a one-day workshop and the same applies to POCUS; longitudinal training with emphasis on image acquisition, interpretation and clinical integration is the key to achieving competency and avoiding untoward consequences. As POCUS expertise among nephrologists is sparse at this time, collaboration with experts from various POCUS-performing specialties (*e.g.*, emergency medicine, critical care) is vital for establishment of robust POCUS training programs with quality assurance measures in place.

CONCLUSION

POCUS is a valuable adjunct to physical examination in patients with cancer and renal dysfunction or fluid/electrolyte disorders. It provides better diagnostic accuracy than conventional physical examination. Proper training is the key to effectively integrate this diagnostic tool into routine clinical practice.

FOOTNOTES

Author contributions: Bhasin-Chhabra B drafted the initial version of the manuscript; Koratala A reviewed, and revised the manuscript for critical intellectual content; Both authors have read and approved the final version.

Supported by Abhilash Koratala reports research funding from KidneyCure and the American Society of Nephrology's William and Sandra Bennett Clinical Scholars Grant.

Conflict-of-interest statement: All the authors declare no potential conflicts of interest.

Country/Territory of origin: United States

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

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

REFERENCES

1 **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]
2 **Russell FM**, Zakeri B, Herbert A, Ferre RM, Leiser A, Wallach PM. The State of Point-of-Care Ultrasound Training in Undergraduate Medical Education: Findings From a National Survey. *Acad Med* 2022; **97**: 723-727 [PMID: 34789665 DOI: 10.1097/ACM.0000000000004512]
3 **Koratala A**, Reisinger N. POCUS for Nephrologists: Basic Principles and a General Approach. *Kidney360* 2021; **2**: 1660-1668 [PMID: 35372985 DOI: 10.34067/KID.0002482021]
4 **Reisinger NC**, Koratala A. Incorporating Training in POCUS in Nephrology Fellowship Curriculum. *Clin J Am Soc Nephrol* 2022; **17**: 1442-1445 [PMID: 36130825 DOI: 10.2215/CJN.09580822]
5 **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]
6 **Abudayyeh AA**, Lahoti A, Salahudeen AK. Onconephrology: the need and the emergence of a subspecialty in nephrology. *Kidney Int* 2014; **85**: 1002-1004 [PMID: 24786870 DOI: 10.1038/ki.2014.29]
7 **Salahudeen AK**, Bonventre JV. Onconephrology: the latest frontier in the war against kidney disease. *J Am Soc Nephrol* 2013; **24**: 26-30 [PMID: 23138480 DOI: 10.1681/ASN.2012070690]
8 **Narula J**, Chandrashekhar Y, Braunwald E. Time to Add a Fifth Pillar to Bedside Physical Examination: Inspection, Palpation, Percussion, Auscultation, and Insonation. *JAMA Cardiol* 2018; **3**: 346-350 [PMID: 29490335 DOI: 10.1001/jamacardio.2018.0001]
9 **Stevenson LW**, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989; **261**: 884-888 [PMID: 2913385 DOI: 10.1001/jama.261.6.884]
10 **Chung HM**, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 1987; **83**: 905-908 [PMID: 3674097 DOI: 10.1016/0002-9343(87)90649-8]
11 **Wang CS**, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005; **294**: 1944-1956 [PMID: 16234501 DOI: 10.1001/jama.294.15.1944]
12 **Torino C**, Gargani L, Sicari R, Letachowicz K, Ekart R, Fliser D, Covic A, Siamopoulos K, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Gueler F, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Siriopol D, Balafa O, Shavit L, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM, Zoccali C. The Agreement between Auscultation and Lung Ultrasound in Hemodialysis Patients: The LUST Study. *Clin J Am Soc Nephrol* 2016; **11**: 2005-2011 [PMID: 27660305 DOI: 10.2215/CJN.03890416]
13 **Cox EGM**, Koster G, Baron A, Kaufmann T, Eck RJ, Veenstra TC, Hiemstra B, Wong A, Kwee TC, Tulleken JE, Keus F, Wiersema R, van der Horst ICC; SICS Study Group. Should the ultrasound probe replace your stethoscope? *Crit Care* 2020; **24**: 14 [PMID: 31931844 DOI: 10.1186/s13054-019-2719-8]
14 **Marbach JA**, Almufleh A, Di Santo P, Jung R, Simard T, McInnes M, Salameh JP, McGrath TA, Millington SJ, Diemer G, West FM, Domecq MC, Hibbert B. Comparative Accuracy of Focused Cardiac Ultrasonography and Clinical Examination for Left Ventricular Dysfunction and Valvular Heart Disease: A Systematic Review and Meta-analysis. *Ann Intern Med* 2019; **171**: 264-272 [PMID: 31382273 DOI: 10.7326/M19-1337]
15 **Spencer KT**, Flachskampf FA. Focused Cardiac Ultrasonography. *JACC Cardiovasc Imaging* 2019; **12**: 1243-1253 [PMID: 31272607 DOI: 10.1016/j.jcmg.2018.12.036]
16 **Mathews BK**, Miller PE, Olson APJ. Point-of-Care Ultrasound Improves Shared Diagnostic Understanding Between Patients and Providers. *South Med J* 2018; **111**: 395-400 [PMID: 29978223 DOI: 10.14423/SMJ.0000000000000833]
17 **Andersen CA**, Brodersen J, Rudbæk TR, Jensen MB. Patients' experiences of the use of point-of-care ultrasound in general practice - a cross-sectional study. *BMC Fam Pract* 2021; **22**: 116 [PMID: 34144701 DOI: 10.1186/s12875-021-01459-z]
18 **Stanley A**, Wajanga BM, Jaka H, Purcell R, Byrne L, Williams F, Rypien C, Sharpe A, Laws P, Faustine L, Leeme T, Mwabutwa E, Peck R, Stephens M, Kaminstein D. The Impact of Systematic Point-of-Care Ultrasound on Management of Patients in a Resource-Limited Setting. *Am J Trop Med Hyg* 2017; **96**: 488-492 [PMID: 27994100 DOI: 10.4269/ajtmh.16-0201]
19 **Munasinghe BM**, Fernando, UPM, Srisothinathan, N, Subramaniam N, Jayamanne BDW, Arulmoli J. Critical care Ultrasonography as a Decision Support and Therapeutic Assist Tool in the Intensive Care Unit: A Single Center Retrospective Survey in a District General Hospital, Sri Lanka. *JPGIM* **8**: E162 1-12 [DOI: 10.4038/jpgim.8332]
20 **Lam AQ**, Humphreys BD. Onco-nephrology: AKI in the cancer patient. *Clin J Am Soc Nephrol* 2012; **7**: 1692-1700 [PMID: 22879433 DOI: 10.2215/CJN.03140312]
21 **Cho S**, Kang E, Kim JE, Kang U, Kang HG, Park M, Kim K, Kim DK, Joo KW, Kim YS, Yoon HJ, Lee H. Clinical Significance of Acute Kidney Injury in Lung Cancer Patients. *Cancer Res Treat* 2021; **53**: 1015-1023 [PMID: 33494125 DOI: 10.4143/crt.2020.1010]

22 **Christiansen CF**, Johansen MB, Langeberg WJ, Fryzek JP, Sørensen HT. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. *Eur J Intern Med* 2011; **22**: 399-406 [PMID: 21767759 DOI: 10.1016/j.ejim.2011.05.005]

23 **Cheng Y**, Nie S, Li L, Li Y, Liu D, Xiong M, Wang L, Ge S, Xu G; EACH study investigators. Epidemiology and outcomes of acute kidney injury in hospitalized cancer patients in China. *Int J Cancer* 2019; **144**: 2644-2650 [PMID: 30426496 DOI: 10.1002/ijc.31993]

24 **Gudsoorkar P**, Langote A, Vaidya P, Meraz-Muñoz AY. Acute Kidney Injury in Patients With Cancer: A Review of Onconephrology. *Adv Chronic Kidney Dis* 2021; **28**: 394-401.e1 [PMID: 35190106 DOI: 10.1053/j.ackd.2021.09.008]

25 **César BN**, Durão Júnior MS. Acute kidney injury in cancer patients. *Rev Assoc Med Bras (1992)* 2020; **66Suppl** 1: s25-s30 [PMID: 31939532 DOI: 10.1590/1806-9282.66.S1.25]

26 **Chorbińska J**, Krajewski W, Zdrojowy R. Urological complications after radiation therapy-nothing ventured, nothing gained: a Narrative Review. *Transl Cancer Res* 2021; **10**: 1096-1118 [PMID: 35116437 DOI: 10.21037/tcr-20-2589]

27 **Koratala A**, Morales Lappot J. Obstructive nephropathy: simple yet complicated! *Intern Emerg Med* 2019; **14**: 315-317 [PMID: 30386975 DOI: 10.1007/s11739-018-1976-x]

28 **Bhasin B**, Koratala A. Ultrasound appearance of the lymphomatous infiltration of the kidney. *CEN Case Rep* 2021; **10**: 150-152 [PMID: 32607679 DOI: 10.1007/s13730-020-00502-9]

29 **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]

30 **Koratala A**. Point-of-care renal ultrasound: the SECONDS checklist. *Clin Exp Nephrol* 2022; **26**: 486-487 [PMID: 35013843 DOI: 10.1007/s10157-021-02171-z]

31 **Bejjanki H**, Koratala A. The TIE fighter sign on point of care ultrasonography. *CEN Case Rep* 2020; **9**: 91-93 [PMID: 31637590 DOI: 10.1007/s13730-019-00428-x]

32 **Bhasin B**, Ber Ce P, Szabo A, Chhabra S, D'Souza A. Correlates and Outcomes of Early Acute Kidney Injury after Hematopoietic Cell Transplantation. *Am J Med Sci* 2021; **362**: 72-77 [PMID: 33812909 DOI: 10.1016/j.amjms.2021.03.013]

33 **Rondón G**, Saliba RM, Chen J, Ledesma C, Alousi AM, Oran B, Hosing CM, Kebriaei P, Khouri IF, Shpall EJ, Popat UR, Champlin RE, Ciurea SO. Impact of Fluid Overload as New Toxicity Category on Hematopoietic Stem Cell Transplantation Outcomes. *Biol Blood Marrow Transplant* 2017; **23**: 2166-2171 [PMID: 28844946 DOI: 10.1016/j.bbmt.2017.08.021]

34 **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]

35 **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]

36 **Galindo P**, Gasca C, Argaiz ER, Koratala A. Point of care venous Doppler ultrasound: Exploring the missing piece of bedside hemodynamic assessment. *World J Crit Care Med* 2021; **10**: 310-322 [PMID: 34888157 DOI: 10.5492/wjccm.v10.i6.310]

37 **Gayen S**. Malignant Pleural Effusion: Presentation, Diagnosis, and Management. *Am J Med* 2022; **135**: 1188-1192 [PMID: 35576996 DOI: 10.1016/j.amjmed.2022.04.017]

38 **El Haddad D**, Iliescu C, Yusuf SW, William WN Jr, Khair TH, Song J, Mouhayar EN. Outcomes of Cancer Patients Undergoing Percutaneous Pericardiocentesis for Pericardial Effusion. *J Am Coll Cardiol* 2015; **66**: 1119-1128 [PMID: 26337990 DOI: 10.1016/j.jacc.2015.06.1332]

39 **Imazio M**, Colopi M, De Ferrari GM. Pericardial diseases in patients with cancer: contemporary prevalence, management and outcomes. *Heart* 2020; **106**: 569-574 [PMID: 31980441 DOI: 10.1136/heartjnl-2019-315852]

40 **Liu RB**, Donroe JH, McNamara RL, Forman HP, Moore CL. The Practice and Implications of Finding Fluid During Point-of-Care Ultrasonography: A Review. *JAMA Intern Med* 2017; **177**: 1818-1825 [PMID: 29059269 DOI: 10.1001/jamainternmed.2017.5048]

41 **Kalantri S**, Joshi R, Lokhande T, Singh A, Morgan M, Colford JM Jr, Pai M. Accuracy and reliability of physical signs in the diagnosis of pleural effusion. *Respir Med* 2007; **101**: 431-438 [PMID: 16965906 DOI: 10.1016/j.rmed.2006.07.014]

42 **Wong CL**, Holroyd-Leduc J, Straus SE. Does this patient have a pleural effusion? *JAMA* 2009; **301**: 309-317 [PMID: 19155458 DOI: 10.1001/jama.2008.937]

43 **Ceriani E**, Cogliati C. Update on bedside ultrasound diagnosis of pericardial effusion. *Intern Emerg Med* 2016; **11**: 477-480 [PMID: 26746413 DOI: 10.1007/s11739-015-1372-8]

44 **Kennedy Hall M**, Coffey EC, Herbst M, Liu R, Pare JR, Andrew Taylor R, Thomas S, Moore CL. The "5Es" of emergency physician-performed focused cardiac ultrasound: a protocol for rapid identification of effusion, ejection, equality, exit, and entrance. *Acad Emerg Med* 2015; **22**: 583-593 [PMID: 25903585 DOI: 10.1111/acem.12652]

45 **Stolz L**, Valenzuela J, Situ-LaCasse E, Stolz U, Hawbaker N, Thompson M, Adhikari S. Clinical and historical features of emergency department patients with pericardial effusions. *World J Emerg Med* 2017; **8**: 29-33 [PMID: 28123617 DOI: 10.5847/wjem.j.1920-8642.2017.01.005]

46 **Cattau EL Jr**, Benjamin SB, Knuff TE, Castell DO. The accuracy of the physical examination in the diagnosis of suspected ascites. *JAMA* 1982; **247**: 1164-1166 [PMID: 7057606 DOI: 10.1001/jama.247.8.1164]

47 **Mercaldi CJ**, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. *Chest* 2013; **143**: 532-538 [PMID: 23381318 DOI: 10.1378/chest.12-0447]

48 **Nauka PC**. GBT: The Focused Assessment with Sonography in Cancer (FASC) Examination, POCUS journal Vol 5 Issue 2, Nov 2020 [DOI: 10.24908/pocus.v5i2.14428]

49 **Doshi SM**, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kidney Dis* 2012; **59**: 222-228 [PMID: 22001181 DOI: 10.1053/j.ajkd.2011.08.029]

50 **Workeneh BT**, Jhaveri KD, Rondon-Berrios H. Hyponatremia in the cancer patient. *Kidney Int* 2020; **98**: 870-882 [PMID:

32497528 DOI: 10.1016/j.kint.2020.05.015]
51 **Berghmans T**, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. *Support Care Cancer* 2000; **8**: 192-197 [PMID: 10789959 DOI: 10.1007/s005200050284]
52 **Seay NW**, Lehrich RW, Greenberg A. Diagnosis and Management of Disorders of Body Tonicity-Hyponatremia and Hypernatremia: Core Curriculum 2020. *Am J Kidney Dis* 2020; **75**: 272-286 [PMID: 31606238 DOI: 10.1053/j.ajkd.2019.07.014]
53 **Bhasin-Chhabra B**, Veitla V, Weinberg S, Koratala A. Demystifying hyponatremia: A clinical guide to evaluation and management. *Nutr Clin Pract* 2022; **37**: 1023-1032 [PMID: 36036229 DOI: 10.1002/ncp.10907]
54 ECRI institute special report: Top 10 health technology hazards for 2020 ecri-top-10-technology-hazards-2020.pdf, last accessed 1/27/2023. Available from: https://assets.ecri.org/PDF/White-Papers-and-Reports/ECRI-Top-10-Technology-Hazards-2020-v2.pdf

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