28850-Answering reviewers:

I. Table (1): Trials concerned with contrast Nephropathy (CIN).

No.	Trial	**Year**	No. of KTRs	Need for HDX	**CIN.**	Comments.
(1)	J.A. Light [8].	**1975**	**34**	Two	**22**	20 patients improved after therapy for "graft rejection".
(2)	Moreau et al, [12].	**1975**	**231**	None	**Nil**	No increase in risk of CIN in KTRs if contrast studies were performed with normal renal function.
(3)	Peters et al. [11].	**1983**	**93**	None	**Very high (84.3%)**	No increased risk was found >120 days post-transplant.
(4)	Ahuja et al, [10].	**2000**	**35**	None	**> 21%**	Patients received *high osmolality contrast*, & **94** % were on CyA therapy.
(5)	Jody et al., [16].	**2015**	**76**	None	**> 13.2 %.**	**CIN** did **not** affect *allograft function* & *survival*, according to the researchers.
(6)	Haider et al [9].	**2015**	**124**	None	**5.6%.**	The largest retrospective study evaluating incidence of CIN in KTRs. Calcineurin inhibitors (CNIs) were being used in 95% patients at the time of contrast administration.
(7)	Bostock et al. [15].	**2016**	40	One.	12.5 %	Renal dysfunction is **3** times more frequent in **KTR** treated with **EVAR**, though overall survival did **not** differ between groups. *Decreased pre-operative eGFR* & ***higher*** *iodine/e GFR ratio* are associated with *post-operative renal dysfunction*.
(8)	Fananapazir G et al, [14]	**2016**	104	None	**7 % & 3 %**	*Incidence of CNI = 7% (7/104) based on a rise of ≥0.3 mg/dL & 3% (3/104) based on a rise of ≥ 0.5 mg/dL. With a strict definition (≥0.5 mg/dL) had a pre-CT eGFR <60 mL/min/1.73 m2. No ptn required DX or had allograft loss 30 days after contrast use.*

II. Finally, it appears that the strict "definition of CIN" in various studies was not universal. While Jody and his colleagues defined CIN as a rise in s. Cr by > **0.3** mg/dL or **25**% rise from baseline within four days of contrast exposure [16], Bostock IC1 and his colleagues defined CIN as an acute kidney injury (AKI) with elevation of S. cr. > **0.5** mg/dL from baseline, or new post-operative hemodialysis (HD) requirement [15]. M. Haider et al 2015, defined CIN as either an absolute rise in serum creatinine of ≥ 0.5 mg/dL or a ≥ 25% drop in estimated glomerular filtration rate (eGFR) after contrast administration [9]. On the other hand Fananapazir G. et al, 2016 [14] applied two definitions for CIN in the most recent study, they found CIN in 7 % based on a rise of ≥ 0.3 mg/dL & 3% based on a rise of ≥ 0.5 mg/dL. Patients with the more strict definition (≥ 0.5 mg/dL) had a pre-contrast eGFR < 60 mL/min/1.73 m^2.

III. "Ultrasound with contrast": Contrast enhanced ultrasound (**CEUS**) is a promising radiological technique with increased popularity. It has a superiority over the color Doppler ultrasound in evaluation of kidney microvasculature studies. A wide variety of diagnoses can be applied including differentiation of cystic from solid lesion, solid mass assessment, pseudotumor and renal artery stenosis. Moreover, CEUS can help in elucidating the hemodynamic changes associated with chronic allograft nephropathy (CAN) [17]. US contrasts are gas microbubbles of nearly the same size of RBCs, which enclosed in a protein, lipid or polymer shell [18]. They last intravascular only for few minutes (time of CEUS examination), after that, the gas exhaled through the lungs and the shell metabolized by the liver [19], so renal excretion is not a possibility. As these contrast agents is not excreted through the kidney, allograft integrity cannot

be deranged. So, their use in KTRs with impaired renal function is completely safe. Furthermore, CEUS is the sole available technique for dynamic evaluation of kidney perfusion, particularly so, when the use of contrast media is mandatory in CT and MR studies in patients with renal dysfunction. CEUS has a wide safety margin in comparison with other radiological modalities [20 & 21].

IV. Up till now, we are sure why renal failure patients are sensitive to contrast utilization. Whether their primary disease is a contributing factor or not, this has to be elucidated by additional future research.

V. Ahuja et al. (2000) also studied 35 kidney transplantation recipients (KTRs).

VI. On the other hand, Fananapazir G, and his colleagues, 2016, declared in the most recent trial that CIN incidence was very low i.e. 7% and 3% according to an elevation of S Cr of > 0.3 and 0.5 respectively, after a low osmolality contrast administration. There was with no need for emergent dialysis or an allograft loss 30 days post-operative [14].

VII. The following precautions are suggested with increased risk of CIN (S. creatinine ≥ 1.5 mg/dL (132 micromols/L) or an eGFR <60 ml/1.73 m2), especially in diabetics:

1) Avoid volume depletion and NSAID [22 & 23].

2) Avoid use of high osmolar agents (1400-1800 mosmol/kg) [24] & [25].

3) Try to use US and MRI without gadolinium contrast, or CT scanning without contrast media when possible.

VIII. References:

[1] Fananapazir G, Troppmann C, Corwin MT, Nikpour AM, Naderi S, Lamba R. Incidences of acute kidney injury, dialysis, and graft loss following intravenous administration of low-osmolality iodinated contrast in patients with kidney transplants. Abdom Radiol (NY). 2016 Jul 5. [Epub ahead of print].

[2] Schwenger V, Korosoglou G, Hinkel UP, Morath C, Hansen A, Sommerer C, Dikow R, Hardt S, Schmidt J, Kucherer H, Katus HA, Zeier M. Real-time contrast-enhanced sonography of renal transplant recipients predicts chronic allograft nephropathy. Am J Transplant. 2006; 6: 609–615. [PubMed].

[3] S. H. X. Morin, A. K. P. Lim, J. F. L. Cobbold, and S. D. Taylor-Robinson, "Use of second generation contrast-enhanced ultrasound in the assessment of focal liver lesions," World Journal of Gastroenterology, vol. 13, no. 45, pp. 5963–5970, 2007. View at Publisher · View at Google Scholar · View at Scopus

[4] D. Cosgrove and M. Blomley, "Liver tumors: evaluation with contrast-enhanced ultrasound," Abdominal Imaging, vol. 29, no. 4, pp. 446–454, 2004. View at Google Scholar · View at Scopus

[5] S. R. Wilson and P. N. Burns, "Microbubble-enhanced US in body imaging: what role?" Radiology, vol. 257, no. 1, pp. 24–39, 2010. View at Publisher · View at Google Scholar · View at Scopus.

[6] F. Piscaglia, L. Bolondi, and Italian Society for Ultrasound in Medicine and Biology (SIUMB) Study Group on Ultrasound Contrast Agents, "The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations," Ultrasound in Medicine and Biology, vol. 32, no. 9, pp. 1369–1375, 2006. View at Publisher · View at Google Scholar · View at Scopus.

[7] Pannu N, Wiebe N, Tonelli M, Alberta Kidney Disease Network. Prophylaxis strategies for contrast-induced nephropathy. JAMA 2006; 295:2765.

[8] Marenzi G, Assanelli E, Campodonico J, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. Ann Intern Med 2009; 150:170.

[9] Kian K, Wyatt C, Schon D, et al. Safety of low-dose radiocontrast for interventional AV fistula salvage in stage 4 chronic kidney disease patients. Kidney Int 2006; 69:1444.
