

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 <i>high osmolality contrast</i> , & 94 % were on CyA therapy.
(5)	Jody et al., [16].	2015	76	None	> 13.2 %.	CIN did <b>not</b> affect <i>allograft function &amp; survival</i> , 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 <b>not</b> differ between groups. <i>Decreased pre-operative eGFR &amp; higher iodine/eGFR ratio</i> are associated with <i>post-operative renal dysfunction</i> .
(8)	Fananapazir G et al. [14]	2016	104	None	7 % & 3 %	<i>Incidence of CNI = 7% (7/104) based on a rise of <math>\geq 0.3</math> mg/dL &amp; 3% (3/104) based on a rise of <math>\geq 0.5</math> mg/dL. With a strict definition (<math>\geq 0.5</math> mg/dL) had a pre-CT eGFR &lt;60 mL/min/1.73 m2. No ptm required DX or had allograft loss 30 days after contrast use.</i>

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  $\geq 0.5$  mg/dL or a  $\geq 25\%$  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  $\geq 0.3$  mg/dL & 3% based on a rise of  $\geq 0.5$  mg/dL. Patients with the more strict definition ( $\geq 0.5$  mg/dL) had a pre-contrast eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>.

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  $\geq 1.5$  mg/dL (132 micromols/L) or an eGFR  $<60$  ml/1.73 m<sup>2</sup>), 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:**

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