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## A systematic review of the relationship between acute tubular necrosis and kidney transplantation

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### ABSTRACT

**Introduction:** Acute tubular necrosis (ATN) is a common syndrome following kidney transplantation. In this study, we reviewed systematically the relationship between ATN and kidney transplantation.

**Materials and Methods:** International databases including PubMed, Web of Science and Scopus were considered for search of English articles by Aug 2019. Seven published articles were finally entered into the study. Keywords were ATN, acute kidney injury, kidney transplantation and renal transplantation or a combination of them in the title/abstracts.

**Results:** There were seven published articles (conducted on 2,534 individuals) reviewed in this systematic review consisted of two retrospective, three prospective studies and two clinical trial studies.

**Conclusion:** The administration of cyclosporine immediately following kidney transplantation is a predicting factor for development of ATN. According to the results, ATN can be associated with kidney transplantation, especially transplanted from deceased donors.

### Implication for health policy/practice/research/medical education:

Administration of cyclosporine immediately following kidney transplantation is a predicting factor for development of acute tubular necrosis.

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### Introduction

Acute tubular necrosis (ATN) is a complex syndrome characterized by a rapid decrease in glomerular filtration rate and consequently retention of metabolic wastes (1). The causes of ATN are multifactorial, which include age of more than 60 years, chronic kidney disease, diabetes mellitus, and length of surgery. Nowadays, due to the high prevalence of ATN and its detrimental effects on body, a great deal of researches to determine the complications of the ATN was conducted. However, few effective modalities for the prevention of the ATN following kidney transplantation were existed. Although the use of calcium blockers, E12 (prostaglandins), theophylline, dopamine, intercellular adhesion molecules, platelet

activating factor, alpha melanocyte-type activating hormone has been repeatedly suggested, no significant results have been obtained (2-9). As mentioned, the length of surgery is associated with the ATN, therefore kidney transplantation is prone to encounter with the ATN. Kidney allograft has some complications such as ATN, rejection of transplantation, allergy, infection and cyclosporine toxicity (10, 11). In this study, we reviewed systematically the relationship between ATN and kidney transplantation.

### Methods

#### Search strategy

In this systematic review, international databases

including PubMed, Web of Science and Scopus were considered for search of English articles by August 2019. All type of articles was included but case series less than five cases report were excluded. Keywords were as following; acute tubular necrosis, acute kidney injury, kidney transplantation, renal transplantation. Sample of search strategy for PubMed can be found in the following sentence.

((((Acute tubular necrosis [MeSH Terms]) OR Acute tubular necrosis [Title/Abstract]) OR acute kidney injury [Title/Abstract]) AND (((Kidney Transplantation [MeSH Terms]) OR Kidney Transplantation [Title/Abstract]) OR Renal Transplantation [Title/Abstract])) AND (“1980/01/01”[PDat]: “2019/07/31”[PDat]))

After collection of articles of interest, references imported to Endnote software and removed duplicate titles. Then, after browsing titles, studies with irrelevant purposes were removed, and then the remaining studies assessed by two independent investigators. The selected studies were performed on humans and published in English.

#### Data extraction

Information dealing with the selected articles (the author's last name, year of publication, study design, sample size and the results of each article were taken by two independent investigators. The differences observed in this process corrected by a third investigator who was independent with the two previous investigators.

#### Results

There were seven published articles (conducted on 2534 individuals) considered in this systematic review which consisted of two retrospective, three prospective studies and two clinical trial investigations. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, a checklist of items that should be included in reports of interventional studies for selected articles (12, 13). The selection process using the PRISMA statement can be seen in Figure 1. The summary of the selected articles was shown in Table 1.

#### Discussion

Evidence shows that ATN is the most common cause of graft failure for up to 50% of transplanted kidneys following the use of cyclosporine (21, 22). Hypoperfusion, cold ischemia times, harvesting, anastomosis, surgical approach and the administration of cyclosporine following renal transplantation are revealed by now about the etiologic causes of ATN (23, 24). Oliguria caused by ATN lasts for two months. In some cases it lasts more than two months and exceeds three months (25). Prolonged ATN happens while cyclosporine is used following kidney transplantation (26). In this regard, the administration

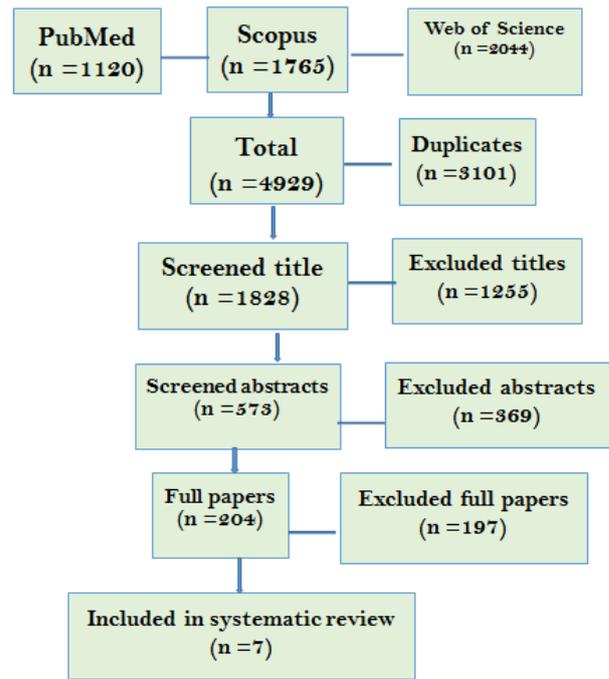


Figure 1. Flow chart of study selection based on PRISMA.

of calcium channel blockers can preserve the acute renal vasoconstriction following the use of cyclosporine (27,28). ATN following kidney transplantation accounts for 90% of acute renal failures which happens within the first weeks after transplantation. It is worthy to be noted that ATN is observed in cadaver transplant recipients in up to 40% of cases. The etiology of ATN is not well-understood. When ATN occurred, patients must undergo daily dialysis and the dose of cyclosporine must be decreased by 50% (29). In the study of Garcia et al, ATN was reported following enalapril administration in two cases. In these two cases, ATN occurred after the administration of cyclosporine-A and also angiotensin-converting enzyme inhibitor (ACEI) to manage hypertension (30). Actually, more reported ATN can be observed among kidney transplantations of deceased donors; hence, it is an effective factor to predict ATN following kidney transplantation (31). In fact, the science of transplantation is young still and needs more research because of its importance and its multiple factors affecting main outcomes related to the health of patients. In the study by Mekeel et al, the effect of rhabdomyolysis was investigated and concluded that rhabdomyolysis is not a contraindication for performing kidney transplantation (32).

#### Conclusion

According to the results, ATN can be associated with kidney transplantation, especially transplanted from deceased donors. As well as, administration of cyclosporine immediately following kidney transplantation is a predicting factor for the development of ATN.

**Table 1.** The detail of reviewed articles in this systematic study

First author	N	Age (y)	ATN	Transplanted from kidney of deceased	Design	Descriptions
Ounissi et al (14)	255	30.1 ± 12.6	N=39 (15.29%)	N=20	Retrospective	<b>Measures:</b> The majority was treated by hemodialysis (79.48%) and half of them were transplanted from kidney of deceased donor. All patients received anti lymphocyte serum and the majority anticalcineurins (69.23%). <b>Conclusion:</b> The ATN is more common among transplanted patients from deceased donors, but it has no impact on patients and graft survival.
Brophy et al (15)	538	-	N=53 (8.8%)	N=121	Retrospective	<b>Measures:</b> A decrease of Azathioprine to 50%, dialysis with strict regional heparin and frequent radionuclide. <b>Conclusion:</b> ATN is a relatively innocent complication.
Hall et al (16)	651	59	N=110 (17%)	N=12	Prospective	<b>Measures:</b> Dialysis <b>Conclusion:</b> This study reveals no significant associations overall between deceased-donor biopsy ATN and the outcomes of graft failure. The potential benefit of more rigorous ATN reporting is unclear.
Ritz et al (17)	190	41 vs. 36	N=30 (15%)	Not reported	Randomized control trial	<b>Measures:</b> Treated by cyclosporine-A (CyA), methylprednisone, and azathioprine. <b>Conclusion:</b> The use of CyA immediately after renal transplantation is a significant factor in the etiology of ATN following kidney transplantation.
Gwinner et al (18)	204	47.9 ± 13.5	N=60 (30%)	N=166	Prospective	<b>Measures:</b> Therapy with interleukin-2 receptor antibodies or with antithymocyte globulin, cyclosporine A, mycophenolate mofetil, prednisolone, ACE inhibitors, AT receptor antagonists, β-blockers, diuretics, calcium channel blockers, α-blockers, nitrates, molsidomine, statins, aspirin, ticlopidine, allopurinol, benzbromarone, insulin, sulfonylurea, vitamin D, bisphosphonates, ganciclovir, valganciclovir, cotrimoxazole <b>Conclusion:</b> ATN is linked to inferior long-term graft function.
Hall et al(19)	635	50 ± 13	N=107 (17%)	N=146	Randomized control trial	<b>Measures:</b> Not reported <b>Conclusion:</b> Procurement kidney biopsy reports of ATN were modestly associated with the, DCD kidney transplantation.
Bagheri et al (20)	61	41.4 ± 13.3	N=12 (20%)	Yes, but frequency was not reported	Prospective	<b>Measures:</b> Dialysis <b>Conclusion:</b> Donor characteristics, organ preservation after harvesting and surgical technique of renal arterial anastomosis lead to severe ATN.

### Authors' contribution

AE, MAM and VR were the principal investigators of the study. VR, DN, NS, RMH and AK were included in preparing the concept and design. RMH, FJ, ET and AA revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

### Conflicts of interest

The authors declare that there is no conflict of interest in this study.

### Ethical considerations

Ethical subjects such as plagiarism and double publication have observed in this study.

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