

Saturday, 21 July 2018

Dear Editor and Reviewers,

Thank you for considering this study for publication in the World Journal of Transplantation. We are grateful for this opportunity. We would also like to thank the reviewers for studying our manuscript and raising some very relevant points.

Please find below our response to each of the points raised:

Reviewer 1:

1. Authors name according with the journal guidelines please use acronym with no period for middle name – *This has been revised. Note that author number 2; Agius-Anastasi is a double barrel last name.*
2. The email address of all authors is not required – *These have been removed. Only the corresponding author email was included.*
3. Correspondent author please provide full name, title, institution, address with city, province/state, postcode and country – *This has been revised.*
4. Please provide ORCID number for authors and information regarding any supportive foundation – *All ORCID numbers are included. No financial support was received.*
5. Minimum of 5 keywords are required – *This was revised. Anastomotic leak, Urinoma/s, Postoperative complications, Ureterostomy, Nephrostomy*
6. “Outline of Surgical and Urological Complications” section: please add more references to the first paragraph if any or insert the one used throughout the paragraph – *Thank you for pointing this out. This has been revised accordingly. See track changes below in red and blue. New references in red.*
7. The part that describes the aspect of a urinoma on US needs reference as well – *This has been revised. See track changes below in red.*

8. Also it is said that US allows “accurate diagnosis of the underlying complication” on paragraph 2, however at paragraph 3 says that “imaging is not very specific in differentiating between different types of fluid collections”. *Thank you for pointing out this inconsistency in our presented argument. This has been revised accordingly. See track changes below in red.*
9. More references are missing along the third paragraph as well. -“Risk Factors and Presentation of Urine Leaks” section – *More references have been added in red.*
10. As with everything in life, prevention is better than cure” should be removed, please – *This has been removed. Thank you.*
11. At the end of “Management of urinary leaks” an extra paragraph could be added to discuss/ summarize the main findings/ proposal of the review for the future. For example, how advances in interventional radiology can minimise problems? - *A new paragraph was added. See track changes below in red.*
12. Is there any other promising future approach to tackle these complications? - *We are not aware of any new approach for treating these complications. Certainly, the literature did not yield any novel procedures. Many of the interventional radiology interventions have been around since the early 2000 era.*
13. Also, it is needed to recognise the limitations of the work – *Very important point. Limitations section added.*
14. ‘Conclusions” section: The last two phrases introduce not or underexplored in the manuscript – *A new paragraph has been added to the discussion section page 8-9.*
15. “Figure” section: title for each figure should follow its number – *These have been altered as per advice.*
16. “References” section: Some references are not in accordance with the journal requirements (7,26, 27, 30) - *All references have been standardised following the journal guidelines.*

Reviewer 2

When the urologic complication is solved by operation or intervention, do you have long-term results of the complication? - *This has been answered in page 8-9.*

...‘This conservative approach has been shown to be successful in a number of retrospective studies, with a success rate varying between 30% and 87%....’

...‘Surgical reconstruction is usually successful in the vast majority of cases. Nonetheless, some patients required more than one surgical procedure for complete resolution...’

We do not have published data of our own transplant centre. However, the vast majority of our patients undergoing surgical reconstruction do well. Searching the literature we found concordant results, vast majority have successful surgical procedure. Below are the retrospective studies describing the success rate of surgical intervention.

Buresley S, Samhan M, Moniri S, Codaj J, Al-Mousawi M. Postrenal transplantation urologic complications. *Transplant Proc.* 2008 Sep;40(7):2345-6. [PMID: 18790231 DOI: 10.1016/j.transproceed.2008.06.036].

Samhan M, Al-Mousawi M, Hayati H, Abdulhalim M, Nampoory MR. Urologic complications after renal transplantation. *Transplant Proc.* 2005 Sep;37(7):3075-6. [PMID: 16213309 DOI: 10.1016/j.transproceed.2005.07.047].

Nie ZL, Zhang KQ, Li QS, Jin FS, Zhu FQ, Huo WQ. Treatment of urinary fistula after kidney transplantation. *Transplant Proc* 2009;41:1624e6. [PMID: 19545693 DOI: 10.1016/j.transproceed.2008.10.103].

Please find below a version of the manuscript (including only the introduction, body, limitations and conclusion) with track changes. The revised manuscript has been submitted as a ‘clean’ version.

Thank you and kind regards,

Dr Jesmar Buttigieg

Outline of Surgical and Urological Complications

Complications in the immediate post-transplant period can be broadly subdivided into vascular, urological, fluid collections and wound healing problems. Vascular complications encompass haemorrhage, thrombosis, aneurysm, dissection and stenosis, whilst urological complications mainly involve leaks and /or obstruction of the collecting system^[4,5]. In essence, haematomas form due to poor tissue handling, insecure knot tying and inadequate haemostasis. The lymphoceles result from severed lymph channels, which should be tied or clipped rather than diathermised, leading to extravasation of lymph. Urine leaks can result in formation of urinomas. These collections can compress vascular structures or urine outflow causing transplant dysfunction. **In addition, urine leaks are associated with increased risk of surgical site infection which can lead to peri-nephric abscesses^[6,7].** Wound healing complications are generally more common when mammalian target of rapamycin (mTOR) based immunosuppression is used^[8].

Ultrasonography is the first-line imaging modality for graft evaluation in the immediate post-transplant period, especially when suspecting vascular problems, fluid collections and/or obstruction^[9,10]. **Apart from being non-invasive, it can provide some additional information on the graft function by measuring the intra-renal resistivity indices^[11]. Differentiating between different types of collections on ultrasound can be difficult.** A urinoma usually appears as a well-defined, rapidly enlarging non-echoic fluid collection without septations, whereas a haematoma usually has a complex and **echogenic** appearance with numerous septations^[9,12]. **Computed tomography may assist in the diagnosis by further elucidating the ultrasound findings such as the extent or exact relationship of the fluid collection to the transplanted kidney^[10].** ^{99m}Tc-MAG-3 radionuclide isotope scan is useful to confirm the presence of a urine leak outside the anatomical space of the urinary tract, as the radionuclide tracer accumulates in the excreted urine as opposed to other type of fluid collections^[13]. A cystogram can provide additional information to establish the exact site of urine leak, especially if it is at the ureterovesical junction (figure 1). Antegrade pyelography performed during nephrostomy tube insertion remains the

investigation of choice to identify the exact site and extent of urine leak. ~~Imaging on its own, however, is not very specific in differentiating between different types of fluid collections, especially between a urinoma and a lymphocele.~~ Ultrasound and /or computed tomography guided needle aspiration followed by biochemical and bacteriological analysis is essential in diagnosing the exact aetiology of fluid collections^[4]. A fluid creatinine which is well above the serum level indicates a urine leak as opposed to a lymphocele which has levels similar to that of serum. Gram stain and cultures are important because any fluid collection can potentially become infected^[6].

Risk Factors and Presentation of Urine Leaks

The incidence of urological complications following kidney transplantation as portrayed in early studies (i.e. including patients between 1970-1990s) ranged between 4.2% to 14.1% ^[14-18], whilst in later studies (i.e. including patients between 1990-2000) ranged between 3.7% to 6.0% ⁽¹⁹⁻²¹⁾. The incidence of urine leaks described in studies which included patients between 1990s and 2000 era ranged between 1.5% to 6.0% ^[19-23]. This variability is probably a reflection of the different transplantation era, diagnostic tools and surgical proficiency. Indeed, the incidence of urological complications has been shown to diminish considerably with increasing centre experience^[24]. These complications are associated with significant patient morbidity, including graft loss and mortality^[17,25].

Urine leaks generally present in the immediate or early post-transplant period (3 months)^[26]. Clinical presentation can include pain and swelling in the transplant area, rising creatinine, oliguria and /or signs of systemic infection^[27]. In the immediate post-transplant period, urine leaks can manifest via the drains or through the wound leading to delayed healing and increased risk of infection^[7,28]. In addition, leaking urine can translocate into the retroperitoneal space, pelvis and occasionally in the pre-sacral and scrotal area^[29]. The leaking of infected urine could lead to peri-

nephric infections and abscess formation. This is important considering that urinary tract infections occur in about 23% of patients receiving a kidney transplant^[30].

~~Most common presentation is transplant dysfunction due to obstruction of important structures by virtue of its mass effect. In addition, excreted urinary molecules can be systemically re-absorbed from extravasated urine resulting in deranged biochemistry.~~

Most urological complications can be traced back to technical errors during retrieval, bench dissection or implantation^[28]. The vast majority of leaks occur at the distal portion of the ureter, most commonly at the site of the ureteroneocystostomy^[26]. Distal ureteral ischaemia and necrosis secondary to compromised blood supply is thought to be the main culprit for early ureteral complications in most patients in the absence of technical difficulties during the transplant operation^[31]. In contrast to the native ureters, which derive their blood supply via both renal arteries and pelvic collaterals, the transplanted ureter depends solely on the blood supplied by the branches of the renal artery that traverse in peri-ureteric tissues. ~~Therefore, it is vital to avoid dissection of the peri-ureteric tissue, especially during laparoscopic living donor nephrectomy.~~ This area, also known as the 'golden triangle' (figure 2), contains important arterial branches, such as the lower polar artery, which supply the distal ureter. Indeed, the importance of preserving the peri-ureteral connective tissue in order to prevent disastrous urinary complications is well documented in the literature ^[14,32-35]. ~~As with everything in life, prevention is better than cure.~~ Male donors, male recipients, African American recipients, Taguchi technique, **graft arterial reconstruction, multiple renal arteries** and recipient **diabetes** were **established as** independent risk factors for urinary complications ^[36-39]. **We believe that gentle handling of the ureter and peri-ureteric tissue, and keeping the length of the ureter as short as possible without tension is of key importance.** A ureter which appears ischaemic after reperfusion should be resected proximally until an adequately perfused area is reached. In this situation, achieving a tension free urinary anastomosis may require special techniques such as ipsilateral uretero-ureterostomy (joining the transplant ureter to the native ureter of that side),

pyelovesicostomy, psoas hitch, Boari flap or fashioning of an ileal ureter in that order of priority. In general, the risk of urinary complications following laparoscopic donor nephrectomy has decreased substantially over time, now comparable to open nephrectomy^[40].

The ureterovesical anastomosis associated with the lowest rate of complications continues to be a subject of debate. The Leadbetter-Politano technique (figure 3) was primarily used in the early days of kidney transplantation^[41]. This has been largely superseded by the less technically demanding Lich-Gregoir technique (figure 4)^[42]. The Taguchi technique (figure 5) has been associated with unacceptably higher incidence of complications compared to the Lich-Gregoir technique^[43,44]. In a recent meta-analysis which included two randomised controlled studies and 24 observational studies, the Lich-Gregoir technique was found to significantly reduce the incidence of ureteral leaks when compared to the Leadbetter-Politano and Taguchi techniques^[45]. The incidence of ureteral stricture and reflux, however, did not differ significantly. The use of a shorter ureter and the avoidance of a separate cystostomy are two hypothetical advantages over the Leadbetter-Politano technique^[46]. A modification of Lich-Gregoir technique, using a short muscular tunnel over the distal ureter, has been shown to reduce complications in two separate retrospective studies^[46,47]. In one Chinese study, primary termino-terminal ipsilateral ureteroureterostomy, was associated with significantly less urinary fistulas when compared to the established Lich-Gregoir technique^[23].

Currently, many centres adopted the routine use of ureteric stent during kidney transplantation. A meta-analysis which included 7 randomised controlled studies, confirmed that routine prophylactic stenting is generally well tolerated and significantly reduce major urological complications^[48]. In a recently published Cochrane database systematic review, it was established that 13 transplant recipients need to be treated (with using JJ stent) in order to prevent one major urological complication^[48]. Despite some opposition due to higher incidence of urinary tract infections, current evidence recommends the routine use of prophylactic stenting.

Management of Urinary Leaks

In general, one can select between two main approaches (**conservative vs. reconstructive surgery**) depending on the site, cause and extent of the leak. **One has to keep in mind that these treatment strategies are not based on robust scientific evidence and tend to vary between centres based on anecdotal experiences. The current best available evidence is merely based on retrospective studies.**

Conservative approach typically involves insertion of a percutaneous nephrostomy followed by antegrade stenting of the collecting system (unless already performed during the transplant operation), together with a Foley catheter replacement. Retrograde stenting of a transplant ureter is technically demanding and often impossible, even by most skilled urologists, because of the atypical position of the ureteric orifice. Antegrade stenting, although generally easier, can still pose technical challenge in absence of pelvi-caliceal dilatation. **Interventional radiologists and transplant surgeons can work together to manage difficult cases^[49].** This procedure diverts the urinary flow away from the leaking site and, thereby, fully decompresses the collecting system in order to allow for healing to take place. The Foley catheter is usually removed once the leak has resolved, ~~whilst the ureteric stent is usually removed endoscopically after about 6-12 weeks.~~ Many centres report stent deployment for a period of 6-12 weeks^[14,33,35,46]. The presence of recurrent urinary tract infection may hasten the time for stent removal.

Surgical exploration is required if urine leak fails to resolve following maximal decompression, especially when dealing with major urine extravasations or necrotic ureters. During the surgical procedure, the necrotic ureter should be resected proximally until healthy tissue is reached, followed by re-implantation. If the remaining viable ureter is short, an ipsilateral uretero-ureterostomy, pyelovesicostomy, psoas hitch, Boari flap or fashioning of an ileal ureter are alternative techniques which could be employed for tension free ureteric anastomosis^[50]. A psoas hitch (figure 6) involves extensive dissection and mobilization of urinary bladder to allow mobilisation towards the transplant ureter, usually up to 5cm. Subsequently the bladder is anchored to the ipsilateral psoas

muscle. Alternatively, a Boari flap (figure 7) can be fashioned to attain an additional 10 cm. If required, this can be used in conjunction with the psoas hitch technique in order to bridge larger gaps between the short transplant ureter and the bladder. Contracted or atrophic urinary bladders in anuric patients seriously limit these options. In this circumstance, an ipsilateral uretero-ureterostomy can be an alternative option if the cause of native kidney failure was not reflux disease. A pyelovesicostomy or an ileal ureter can be fashioned, the latter being preferred for larger gaps, in situations where no donor or recipient ureter can be salvaged^[51]. Both these techniques are devoid of an anti-reflux mechanism. Some patients may require more than one surgical procedure in order to correct the underlying problem^[23]. In all cases, serial ultrasound examinations together with close monitoring of the transplant excretory function is of chief importance in order to anticipate any secondary ureteral strictures.

Traditionally, urine leaks have been corrected by open reconstruction. Over the last two decades, advances in interventional radiology have allowed several patients to be effectively managed percutaneously, avoiding the morbidity associated with open surgery^[49,52]. This conservative approach has been shown to be successful in a number of retrospective studies, with a success rate varying between 30% and 87%^[19,21,53-55]. This considerable inter-centre variability is probably related to different baseline characteristics. We believe that the outcome largely depends on the aetiology, site and extent of the urine leak. In general, small leaks at the ureter implantation site tend to do well with conservative management, whilst extensive leaks especially if related to ureter necrosis do better with open surgery. When in doubt we treat conservatively in the first instance and then proceed to surgical reconstruction only if the patient fails to respond. The type of surgery is frequently dictated by the intra-operative findings and the overall state of the patient. Surgical reconstruction is usually successful in the majority of cases^[19,21,23,55]. Nonetheless, some patients required more than one surgical procedure for complete resolution ^[23].

Limitations

This narrative review is intended to provide a general overview of the early urological complications after kidney transplantation. Although we performed an extensive literature search, this review lacks the scientific rigour of article selection found in a systematic review and therefore susceptible to selection bias. In addition the selected articles have not been subjected to quality evaluation.

Conclusions

Urological complications, especially urine leaks, remain the commonest type of surgical complication following kidney transplantation. The preservation of peri-ureteric tissue during kidney retrieval, employing the Lich-Gregoir ureteroneocystostomy technique and routine prophylactic ureteral stenting have been associated with lower incidence of such complications. Serial ultrasound examination of the transplanted graft in the early post-operative period is of key importance for early detection of these potential complications. ~~Urine leaks have been traditionally corrected by open reconstruction. However, advances in interventional radiology have allowed several patients to be effectively managed percutaneously, avoiding the morbidity associated with open surgery.~~ The first line management of urine leaks is usually percutaneous urinary decompression. Failing this approach, surgical intervention is usually required, especially if dealing with major leaks or necrotic ureters. Although urological complications are associated with significant morbidity and occasionally mortality, the prognosis is generally excellent if recognised and treated successfully in a timely manner.