# PROGRESS IN PEDIATRIC UROLOGY IN THE EARLY 21ST CENTURY

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# PROGRESS IN PEDIATRIC UROLOGY IN THE EARLY 21ST CENTURY

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This collection of articles covers important topics in Pediatric Urology and the progress made in these areas in the early 21st century. This book is dedicated to our teachers and trainees who gave us the necessary impetus to continue to improve and seek answers to unsolved problems.

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EDITORIAL
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# Editorial: Progress in Pediatric Urology in the Early 21st Century

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**Keywords: Pediatric Urology, Bladder Exstrophy, Neurogenic incontience, Laparoscopic surgery, Enterocystoplasty, tissue engineering, pediatric urolithiasis, bladder dysfunction**

**Editorial on the Research Topic**

**Progress in Pediatric Urology in the Early 21st Century**

The intention of this Research Topic was to compile a collection of articles outlining areas of progress in pediatric urology since the onset of the twenty-first century. Some important topics, such as DSD, proximal hypospadias, and robotic assisted surgery were deliberately excluded since they have been the subject of recent Research Topics in Frontiers in Pediatrics. In the end we chose to cover laparoscopy, bladder exstrophy, urolithiasis, urethral strictures, and management of neurogenic incontinence, tissue engineering and the use of bowel in reconstruction. Finally, we were privileged to enlist Prof. Philip G. Ransley to express his thoughts on the future of the specialty. All of the senior authors of the articles included have an impressive track record on their fields. We are sure the readers will profit from reading this collection.

## APPLICATIONS OF LAPAROSCOPIC SURGERY IN PEDIATRIC UROLOGY

Szavay reviewed the topic of laparoscopic procedures in the pediatric urinary tract. Laparoscopic surgery, and reconstructive surgery in particular is a late twentieth and early twenty-first century development in pediatric urology. Beginning with the publication of the first pediatric laparoscopic pyeloplasty (LP) in 1995, the last 24 years have seen this procedure become the first choice of many surgeons to treat ureteropelvic obstruction in children of all ages. Mastery of laparoscopic suturing techniques requires good mentoring, a rather long learning curve and most of all the conviction that the effort is worth pursuing. The advantages of minilaparoscopy (using 3 mm working ports and a 5 mm umbilical port for the camera and to introduce the sutures) are not only cosmetic but results in superior outcomes with a negligible reoperation rate. Rapid recovery and minimal morbidity are the hallmarks of mini LP. Of course the availability of robot-assisted procedures with allegedly equal outcomes and much easier to master, has lured many surgeons away from learning the more demanding mini LP. Nevertheless, the need for 4 ports, the much larger trocars and the infinitely higher cost of robotic assisted surgery, not to speak the limited availability outside the more affluent centers, makes the learning of mini LP procedures a must for training the next generation of pediatric urologists.

The review by Szavay is limited to transperitoneal procedures. We do not consider this a shortcoming since in our practice, retroperitoneoscopic procedures have no place. Others continue to use retroperitoneoscopy arguing that in traditional urological open procedures the retroperitoneal approach is preferred. Theoretical advantages include less risk of injury to intraperitoneal structures and of development of adhesions. The price to pay is operating

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with the patient in the flank position, the use of larger trocars or incisions to create the working space,reduced visibility and a restricted working space in small children. In practice, after hundreds of cases of transperitoneal renal procedures, we never had a visceral or vascular injury and in reoperative cases, no or minimal adhesions are observed.

Other, both ablative and reconstructive procedures are well reviewed in this article.

## RECENT TRENDS IN THE MANAGEMENT OF BLADDER EXSTROPHY: THE GORDIAN KNOT HAS NOT YET BEEN CUT

This article from authors from Regensburg, Germany, led by Promm and Roesch focuses on the problem of the initial management of bladder exstrophy. With a thorough review of the literature, the authors tend to advocate a delayed closure, complete repair (including the epispadias) and no osteotomies. We wholeheartedly agree with their conclusions with minor exceptions. The advantages of delayed primary repair are obvious. The procedure need not be treated as an emergency, the best team of surgeons and anesthesiologists can participate and the failure rate in terms of dehiscence is not increased compared to neonatal closure. Also the waiting time gives the parents to seek other opinions and choose the center of their liking for the primary repair. We agree that osteotomies are not helpful in classical exstrophy cases since the initial success of a correctly done closure without osteotomies approaches 100% and there is no good evidence in the literature that either continence or sexual function are improved by them. Although we always do a complete repair in females, we have abandoned the complete repair in males in favor of closing the bladder and proximal urethra at the initial closure leaving the epispadias repair for a second operation. In our opinion, this method reduces the risk of penile ischemic damage. The authors of this review conclude that: "Further, clinical research should focus on multi-institutional collaborative trials to determine the optimal approach."

## EFFECTIVENESS OF PRENATAL INTERVENTION ON THE OUTCOME OF DISEASES THAT HAVE A POSTNATAL UROLOGICAL IMPACT

Authors from Berlin and Hanover contributed a minireview on the published articles reporting outcomes of prenatal intervention for diseases that have an urological impact after birth (Bañuelos et al.). The review focuses mainly on LUTO, congenital adrenal hyperplasia, and myelomeningocele. The published reports provide evidence that in severe fetal bladder outlet obstruction in the second trimester, effective and lasting decompression allows survival in an otherwise almost invariably lethal situation, mainly thanks to improved lung development. It remains unclear if renal or bladder function are improved in the long term. Problems continue to be related to the near impossibility of conducting prospective randomized trials and shortcoming with instrumentation. Whether the time proven shunting with its many potential complications will eventually be replaced by fetoscopic procedures remains to be seen. Available information suggests that in the long term renal function is not improved (1) therefore the decision to intervene in the fetus with LUTO remains up to very well informed parents.

The fetal closure of myelomeningoceles seems to reduce the incidence of hydrocephalus and thus the need for shunting, an important cause for long term morbidity and mortality in spina bifida patients. Published reports offer conflicting results regarding the potential benefits of fetal closure with regards to bladder function. The answer will become clear in time when large numbers the operated patients reach mid childhood and bladder function can be evaluated more accurately than in infants.

Finally, the prenatal treatment with steroids of female fetuses at risk for being affected by congenital adrenal hyperplasia (with a positive family history) is entering a new era thanks to the possibility of making the diagnosis and determining the sex of the fetus on maternal blood sample before an amniocentesis can be performed. This will obviate the need to treat a large number of fetus who do not treatment either because they are not affected or males, since to be effective to prevent virilization, dexamethasone needs to be started before the 8th gestational week.

## UPDATE ON SURGICAL MANAGEMENT OF PEDIATRIC UROLITHIASIS

Sultan et al. from Karachi wrote an exhaustive review of current interventions to treat pediatric urolithiasis. They describe in detail current minimally invasive techniques used to treat stone in children. The strong point of this article, which reflects the enormous experience of the authors at the Sindh Institute for Urology and Transplantation, is the author's conclusion that: "Thus this manuscript guides how to select the least invasive option for an individual patient, considering age and gender; stone size, location and composition; facilities and expertise available."

## USE OF BOWEL IN PEDIATRIC RECONSTRUCTION

The group from Manheim led by Stein et al. wrote an excellent review about the use of bowel in pediatric Urology. Despite the optimistic view that the use of bladder augmentation is becoming rare thanks to the success of non-operative methods to deal with diminished bladder capacity and compliance, centers dealing with large numbers of patients with spina bifida and bladder exstrophy still perform bladder augmentations or continent diversions rather frequently. As is the case with many reconstructive procedures, past experience and different interpretation of published data often leads to different practices by different surgeons. We personally use preferentially the sigmoid colon unless there are compelling reasons not to. The concept that the urodynamic results using sigmoid are

not as good as with ileum stems from the popularization in some textbooks of incorrect methods to reconfigure the colon. When the sigmoid is reconfigured as Goodwin described the reconfiguration of the small bowel (2), the results are excellent with the additional advantage the use of sigmoid colon does not cause any potential metabolic or digestive problems and the incidence of post-operative bowel obstruction caused by adhesions is lower (3). We continue to avoid the use of the ileocecal segment also because its elimination from the gastrointestinal tract causes an acceleration of the intestinal transit that may impair fecal continence in patients with neurogenic bowel (4, 5).

The authors are correct in stating that the use of seromuscular colocystoplasty lined with urothelium has not gained wide acceptance. However, despite limited indications it plays an important place in the armamentarium of some pediatric urologists (6) and it avoids the potential metabolic consequences of intact bowel segments in properly selected cases.

## TRAUMATIC POSTERIOR URETHRAL STRICTURES IN CHILDREN AND ADOLESCENTS

Podesta and Podesta from Buenos Aires were asked to review the topic of pediatric traumatic posterior urethral strictures based on their vast experience and their published work. The review gives a comprehensive overview of the surgical options to correct traumatic posterior urethral strictures in children based on anatomical findings. These lesions, fortunately rare in the western world, are more common in other parts of the world. The authors recommend a classical approach to the initial management with suprapubic cystostomy and delayed repair for complete disruptions. They clearly indicate situations in which a primary realignment is recommended. They clearly describe the perineal approach, maneuvers to gain anterior urethral length and the indications for the transpubic approach. Although one of us has used and published experience with endoscopic reestablishment of urethral continuity and the classical transpubic approach described by Pierce and Waterhouse several decades ago, we now use primarily the perineal approach and now fully subscribe to the authors view that: "the progressive perineo-abdominal partial transpubic anastomotic repair has advantages over the isolated perineal anastomotic approach in patients with "complex" PFPUDD. This approach provides wider exposure and facilitates reconstruction of long or complicated posterior urethral distraction defects."

## ANTERIOR URETHRAL STRICTURES IN CHILDREN: DISEASE ETIOLOGY AND COMPARATIVE EFFECTIVENESS OF ENDOSCOPIC TREATMENT VS. OPEN SURGICAL RECONSTRUCTION

The pediatric urology group in Hamburg (Vetterlein et al.) addressed the topic of anterior urethral strictures in children. In pediatrics, most anterior urethral strictures are iatrogenic or traumatic. The important message of this review is that urethroplasty is far superior to endoscopic procedures are rather ineffective in the long-term. They reach the important conclusion that open surgical reconstruction: "should be preferred to avoid multiple, repetitive interventions." We wholeheartedly agree with this conclusion.

## SURGICAL MANAGEMENT OF NEUROGENIC SPHINCTER INCOMPETENCE IN CHILDREN

Authors from Hanover and Berlin (Ludwikowski et al.) contributed a literature review of results of surgical methods to treat neurogenic sphincteric incontinence. They conclude that injection of bulking substances to the bladder neck or proximal urethra as well as surgical methods to reconfigure the bladder outlet are of little practical value. Effective published methods include bladder neck sling in girls, artificial urinary sphincter implantation in both sexes and bladder neck closure. Unfortunately, as also reported by others, the level of published evidence is low.

## TISSUE ENGINEERING IN PEDIATRIC BLADDER RECONSTRUCTION—THE ROAD TO SUCCESS

Horst et al. from Zurich describe the current state of research on tissue engineered bladders. This and many other groups are making steady but painfully slow progress toward reaching the goal of creating tissue suitable for use as a bladder wall substitute. The obstacles are formidable particularly relating to vascuarization and innervation of the implant. The transfer of tissue from the laboratory construct to a large animal continues to pose enormous challenges. Unfortunately the much publicized trial (7) which ultimately failed was directed at the wrong population. Obviously, the problem with myelomeningocele is the central and peripheral nervous system, not the target organ, the bladder. Even if a normal bladder could be constructed in the laboratory in this patient population it would have no greater chance of success than implanting a new leg that has abnormal innervation. Nevertheless, these research efforts are certainly worth pursuing since the knowledge acquired is enormous and will eventually yield useful clinical applications.

## DIAGNOSIS AND MANAGEMENT OF BLADDER DYSFUNCTION IN NEUROLOGICALLY NORMAL CHILDREN

The group from Salvador de Bahia led by Fuentes et al. presented a review of this topic in a clear and detailed fashion. Non-neurogenic bladder dysfunction is one of the most frequent problems confronting the pediatric

urologist in everyday practice and is a confusing topic for the inexperienced. This article is very didactic and should serve as a guide for many starting a pediatric urological practice.

## THE FUTURE OF PEDIATRIC UROLOGY

Ransley with decades of experience and a leader in the field, shares with us his view of our specialty in the decades to come with the inevitable progress in robotic surgery and artificial intelligence, thus completing this update of progress in pediatric urology in the early twenty-first century.

We are grateful to all who contributed so generously to this effort and hope the readers will enjoy and profit from this articles as much as we did.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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OPINION
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# The Future of Pediatric Urology

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It is a slightly prejudiced view from the inside, but there seem to be few specialities which encompass such a wide and divergent range of conditions that we in pediatric urology are faced with almost every day of our working lives. As a consequence, we are exposed to and have to accommodate advances in many different areas of medicine from endocrine treatment of the fetus to exploring the limits of robotic surgery. I am not sure of the wisdom of asking a long retired pediatric urologist to speculate on the future of the speciality but then no-one can look forward with any certainty. In some ways we are programmed to resist change and sometimes we are just not able to grasp the significance of what we are being told. It is with some personal embarrassment that I recall reading the very first papers describing the theoretical possibility of extracorporeal shockwave therapy for renal stones and thinking to myself that "this can never catch on"! However, I am in good (or bad!) company. The embattled resistance to Lister's antiseptic technique by much of the profession for so many years reflects a corporate blindness which we still potentially suffer from today although modern communication alleviates this to some degree. In many ways a professional lifetime is like a journey in a fog. We have limited vision. The way ahead is shrouded in mist and far from clear but slowly appears as one moves forward while what we experienced in the past is swallowed and lost in the mists of time.

At the basic level of our surgical lives is surgical technique which has undergone steady refinement over centuries and decades with the occasional boost given by a conceptual breakthrough. The steady improvement in results from advances in suture material was a passive benefit but the conceptual advance of enlarging the bladder using bowel was ahead of its time and doomed to failure until the game-changing process of intermittent catheterization came to its rescue. I can remember reading the notes of a patient who had a colocystoplasty in 1966, less than a decade before CIC was introduced and became widespread. The anticipation and optimism shone through in the early pages but the dismal outcome and evolution to a classical conduit was equally well documented. That is the problem about trying to see the future. Some developments are the result of dogged years of background work, like transplantation, while others blossom from something not visualized before like ESWL or CIC. And yet, our innovative surgeon couldn't see what lay ahead, however simple. That is how I feel as I write. How can I introduce you to the things I cannot see!

The Mitrofanoff channel was another of those eureka moments and one has to say that the combination of sutures, CIC and a Mitrofanoff conspired to revolutionize our current practice of reconstructive pediatric urology. But if that was our lunar landing, we still yearn for Mars.

The advances in tissue engineering and command of stem cell differentiation may yet deliver for us the tissues that we long for. We know that the progress is slow, and the practical difficulties are great, but we can feel that an alternative to the use of bowel in the urinary tract is on the horizon and perhaps direct urethral substitution will become a possibility, but it is not here and now nor any time soon. It is with this in mind and with my future blindness that I have always tried to leave healthy, if non-functional, tissue behind in case it may be valuable as a cellular source in years to come. However, it is likely that in a manner similar to tissue created in culture for the treatment of burns, stem cells may be able to deliver small quantities of homologous tissue grown in the lab for reconstruction by conventional techniques. I am thinking of urethral reconstruction in the hypospadias cripple as the commonest challenge that would benefit greatly from this tiny

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incremental progress. It will be expensive and labor intensive, but it may open the door to a new world where tissue availability is no longer an issue. But it is others, not us at the coal face who will make the essential progress that we can put to good use.

The analysis of the human genome was released with a fanfare that promised much and genetic studies continue to probe the factors underlying everything we see and do. For a surgical simpleton like myself I thought only in terms of understanding congenital anomalies and although candidate genes have been identified for some conditions, the way to exploit such knowledge is not clear. However, the functional implications of genetic abnormalities are much more important such as the vulnerability to urinary infection or the development of embryonal tumors. If, as has been suggested, Wilms' tumor develops due to low activity of a gene responsible for maturing kidney cells, and that gene could be activated to suppress the tumor, we enter a magical world beyond my understanding.

The world of transplantation has grown enormously since the first renal transplant more than half a century ago and thanks to the sophisticated advances in immunosuppression has taken on an almost routine nature. The expansion of this world into liver, face and limbs has little impact on pediatric urology but what about the uterus and genitalia? It is early days as yet, but the first baby from a fertilized egg implanted into a transplanted uterus has been born. Far from a routine, what happens if it becomes more widely applicable? In circumstances where potential fertility is part of the assessment and decisional judgment, will we have to consider potential uterine transplantation on one side of the equation? War is recognized as a great stimulant to innovation and sadly landmine injuries took their toll of external genitalia which is now being addressed by genital transplantation. Will that too cascade down into pediatric urology and be part of our discussion in very severe genital anomalies?

Technology surrounds us in everyday life and artificial intelligence beckons. We are living in a world where simple thoughts can be transferred from one individual to another when both are wearing EEG caps and the signals are analyzed by AI. If only we could communicate with our trainees that way! But maybe AI can be trained to recognize a full bladder and take whatever action is appropriate. Combining technology with stem cell expertise is already promising an implantable kidney whereby sheets of differentiated renal tubular cells are perfused by blood. It will be a shame if such spectacular progress is thwarted by the difficulties of transporting the "urine" produced to the bladder in a conduit of artificial material.

Of course, on a more prosaic level the technological advance which impacts all of us in everyday life is the development of robotic assisted surgery. We are all familiar with its potential and its boundaries are being extended almost daily. A new skill set is required which the younger generation are completely at home with, but we have not yet exploited the very reason that the system was developed which is remote surgical intervention which would challenge some of our classical understanding of responsibility in surgical intervention. Similarly, we may be challenged by the idea of a robot technician (still a human one as far as my myopic vision goes) who is trained to do some repetitive tasks well such as suturing a long anastomosis.

All of these amazing prospects are very largely dependent on the investment, skills and commitment of others outside our world of pediatric urology with whom we collaborate, ready to bring their advances "to the table" when the time is right. We can do little to assist their progress but maintain a dialog and be ready when the time comes. This should cause us to take a good look at ourselves and whether we are in the best condition possible to face what the future brings. The one thing that is clear in my mind is that the future of pediatric urology lies in some reorganization of our structure. First of all, we need to look at what has happened to pediatric urology. From tentative early beginnings pediatric urology has expanded enormously and independent units have grown up in almost every university hospital. There are now over 1,000 fellowship trained pediatric urologists in the United States and when the British Association of Pediatric Urologists was founded the 10 members could sit round a table. At the last meeting I went to there were, I think, more than 70 people. A combined European and American pediatric urology meeting can now attract over 1,000 delegates. The early pioneers in the speciality would be flabbergasted. In some ways this is wonderful news and parents can bring their children to a specialist with ease. However, this expansion has coincided with a significant change in our potential workload, at least in the western world. I have to say that my comments are really based on the experience and demographics of the western hemisphere although heavily influenced by two decades of experience in south Asia.

We have built the fundamentals of a pediatric urological service on expertise acquired from treating large numbers of patients with a limited number of conditions. Numbers are important whether it be for maintaining a personal level of expertise or training the next generation and the less common the problem the more important numbers become. There are a limited number of conditions in our speciality such as the Exstrophy/Epispadias complex, the cloacal anomaly spectrum, bilateral single ectopic ureters and the prune belly syndrome which require huge experience and immense technical skill to maximize the quality of life with minimal intervention. On reflection, I would include the ectopic ureterocoele in this list. The prolonged suffering of these unfortunate children through serial unsuccessful interventions is sadly still a common occurrence today. These are conditions which for the moment depend entirely on our collective experience and individual surgical skill. Although intense studies continue into the genetic or epigenetic background to these conditions, we cannot see any preventative solution arriving any time soon and the need to maintain our skill levels remains paramount. Even relatively common conditions such as posterior urethral valves require the in-depth resources of an expert unit to manage them well as they present management challenges from so many different facets of the stressed urinary tract. Managing a high urine volume from a dilated upper tract draining into a bladder which may change from being of low volume, poorly compliant and hypercontractile to being an acontractile floppy bag requires an understanding which comes only with the experience of large numbers, and the crises are intensified as transplantation looms.

Unfortunately, the expansion of our speciality in terms of centers as well as individuals has coincided with a downward trend in the numbers of patients with serious congenital anomalies. One of the simple factors is simply the declining birth rate. Whatever the social or economic factors are in driving this trend, it is a simple fact that birth rates have almost halved in the last 5 decades following the post-war boom. My generation was privileged to witness and participate in the introduction of pre-natal diagnosis, another example of progress in which we were the recipients rather than the instigators of progress and honestly, I believe that we were not active enough in entering the prenatal world in the early days. This is changing now as the pediatric urologist brings the technological advances of miniaturization of endoscopic instruments and laser fibers to the field. Prenatal diagnosis was a revelation and we are still only beginning to understand the kaleidoscope of events which can ultimately lead to the post-natal state with which we are familiar. On thing which I can see through the fog is that in a generation or two we will have a better handle on intra-uterine obstruction and the benefits (or not) of intervention on renal or bladder outcomes. However, in the meantime prenatal diagnosis has brought with it the two-edged benefit of termination. Not surprisingly this is a contentious issue with many conflicting personal, religious and political philosophies but the fact is that termination has added to the reduction in severe structural anomalies entering the postnatal world. The high termination rate for trisomy 21 and severe cardiac anomalies automatically reduces the number of patients with associated genito-urinary anomalies. The urologically specific termination of severe outflow obstruction or structural abnormality such as cloacal exstrophy, is more limited due to the lack of specificity, but nevertheless has brought about a significant drop in the number of cases requiring the post-natal expertise a pediatric urologist can bring.

It is clear to me that this combination of rapid expansion and reduced complex workload is a lethal cocktail for the maintenance of standards, surgical advancement, or training of the next generation. Complex pediatric urology can no longer be spread thinly, dictated by the randomness of populations but for the future we will have to accept and embrace wholeheartedly the concept of centralization of expertise for specific conditions. Without this we will start going backwards. Some centralization occurs serendipitously perhaps dictated by geography or politics but one of the first efforts to do this was undertaken in the United Kingdom in the 'nineties for the management of the Exstrophy/Epispadias complex so that only two centers in England and Wales are responsible for these conditions. It didn't happen overnight but came after several years of debate between the members of the British Association of Pediatric Urologists. Once a professional accord had been reached, the decision was taken to the Ministry of health and activated. This, of course, was relatively easy to do within a nationalized health system but the important principle was that this had been a professional decision communicated to the administration. This is how it should be, and I fear that if we do not acknowledge the changes that are occurring it will be the administrations that will in time impose their own decisions. There have been other attempts to address the same problems by other means and avoid what some see as the inverse stigma associated with centralization. One of these was the consortium convened in the eastern United States where the patients remained fixed but the surgeons from three institutions traveled in order pool and gain experience collectively. It works and has many benefits, but it is administratively cumbersome and insanely expensive. It is good that it is happening even if only to highlight the need which has brought it into being.

In some ways pediatric urology is following the trends seen in adult urology. The changes in surgical practice in one of our parent specialities has given rise to the situation in which the majority of urological workload is outpatient based. In Pediatric urology the rise in the investigation and treatment of bladder dysfunction, the influx of large numbers of cases detected by prenatal ultrasound but not requiring surgical intervention and the demise in surgical intervention for reflux combined with the reduction in complex anomalies has given rise to a similar situation. I am reminded of an occasion experienced while performing an open partial nephrectomy for a renal tumor as a visiting surgeon. One of the observers was an urology resident who had come to see it partly because he said that in his 4 years of urological residency, he had yet to see a kidney other than through a telescope! Life changes but our speciality needs to maintain a core of advanced surgical skills.

Our profession already accepts centralization for complex problems. Pediatric cardiac surgery, Liver transplantation, rare tumors, and fetal intervention are already areas which are centralized in many parts of the world. We have enjoyed an explosion in interest and expertise in pediatric urology but now is the time to reflect and consolidate our position. The hub-and-spoke model seems to fit our needs admirably. Consultations and routine interventions can take place locally to the benefit of young families, but the complex material is transferred centrally within the same team. Such a system concentrates data, provides for surgical mentorship and the development of a hierarchy for the training and development of the young surgeon while maintaining expertise through numbers. It is a win-win situation.

It is possible that even with a hub and spoke system each center may not receive enough cases to maintain expertise. It has become the authors firm conviction that we need to begin to see pediatric urology as a global cause, a global family. This feeling comes about from the privilege I have had of working in Pakistan over the last 20 years. This collaboration began in the classical way as a visiting fireman but as the years went by the relationship changed and I was able to draw on their enormous workload and experience. I can honestly say that I was a much more experienced and arguably a better reconstructive surgeon after 10 years of working in Pakistan three times a year than I was at the end of 30 years of full-time experience in London. The populations of many parts of the world including most of Asia, Africa and S. America have not seen the dramatic reductions in birth rate experienced in the West and prenatal diagnosis has not yet had any significant impact in many places. If, at this moment the expertise lies in the West but the babies who

need that expertise are in the East then the conclusion is obvious, and it will be important to act before that expertise declines. As I peer through the fog, I can see vague shapes of the future coming into view. Every major center of Pediatric Urology in the West has established a formal link with a similar institution for mutual benefit. Each brings different dishes to the feast. On one side there are centuries of academic discipline, modern surgical development and rigorous training. They are complemented by patient numbers, new challenges and experience. Of course, any such system has to be mutually beneficial but that is not too difficult to envisage although it will require some change in attitude both on the part of our profession and those who administer us. However, the opportunities it opens up for training in both the routine and the exotic and the self-development of the experienced surgeon are truly wonderful. It is likely that any pediatric surgical sub-speciality will have to adopt the same course of action. Many institutions have taken the first tentative steps in this direction, but our campaign has to be to make it mainstream.

If, in desperation, I turn to radar to peer ahead, I can envisage a cure for cancer. I can see artificial blood. I can imagine that I see an implantable artificial kidney. I am sure that I recognize miniaturized robotic instruments controlled by AI and I think I can see tissue engineering coming to the aid of my grandchildren. My surgical life has contributed nothing to this progress but what I see clearly now is that experience is essential for expertise in a surgical speciality and that the future of pediatric urology lies in worldwide cooperation and that now is the time to begin making it happen.

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The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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# Effectiveness of Prenatal Intervention on the Outcome of Diseases That Have a Postnatal Urological Impact

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We reviewed the literature addressing outcomes of fetal intervention of conditions that require post-natal urological management including lower urinary tract obstruction, hydrometrocolpos, congenital adrenal hyperplasia, and myelomeningocele. Despite several decades of fetal intervention for these conditions, benefits remain elusive in part because of the enormous difficulty of conducting prospective randomized studies. In this review, we reached the following conclusions:

1. Prenatal intervention in lower urinary tract obstruction (LUTO) improves survival in the worst cases by improving pulmonary function and it may be advantageous for renal function, particularly in patients with adverse urine parameters.
2. Prenatal treatment of female fetuses at risk of having congenital adrenal hyperplasia (CAH) reduces virilization. Non-invasive fetal DNA analysis allows earlier diagnosis, reducing the risk of treating with dexamethasone males and non-affected fetuses.
3. Fetal treatment of myelomeningocele (MMC) is gaining momentum. Prospective studies including standardized urologic evaluation will determine if the encouraging results reported by some hold on the long term follow-up.

**Keywords: LUTO, congenital adrenal hyperplasia (CAH), vesicoamniotic shunt, myelomeningocele, fetal therapy, posterior urethral valves**

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## INTRODUCTION

The purpose of this minireview is to present current knowledge of the effectiveness and impact of prenatal intervention in fetuses with congenital anomalies which have urological consequences in postnatal life. Prenatal detection of genito-urinary tract anomalies has been possible for about 50 years and prenatal surgical interventions for lower urinary tract obstruction (LUTO) date back to the 1980s (1). Significant technical improvements in ultrasonography (US) technology and the addition of fetal MRI have led to significant refinements in prenatal diagnosis. In addition, fetal genetic testing has allowed the prenatal diagnosis of many diseases, among them congenital adrenal hyperplasia (CAH) the prenatal treatment of which impacts postnatal management and outcome. Nevertheless, prenatal treatment of many conditions diagnosed prenatally remains controversial. Here we briefly summarize the current literature regarding prenatal management of fetal lower urinary obstruction, hydronephrosis, hydrocolpos, congenital adrenal hyperplasia, and myelomeningocele.

## METHOD

Literature review searching PubMed, Cochrane, and Embase databases using pertinent key words for each subject of this review. Articles from the last 10 years were preferentially included for this review. Older articles were included if considered important.

## RESULTS

### Lower Urinary Tract Obstruction (LUTO)

Fetal LUTO refers to the combination of bilateral hydroureteronephrosis and a persistently distended bladder (2). It occurs in 2.2/10,000 pregnancies (2). Fetal LUTO in the second trimester of gestation can lead to postnatal renal failure as well as early respiratory insufficiency due to pulmonary hypoplasia resulting from diminished or absent amniotic fluid. The principal causes of LUTO are posterior urethral valves, Eagle Barret syndrome (prune belly syndrome or PBS) and urethral atresia (3). The mortality of fetus with bilateral hydronephrosis, a distended bladder and oligo- or anhydramnios in the second trimester of life approaches 100% without intervention. End stage renal insufficiency will affect a high proportion of surviving fetuses leading to dialysis and the need of a transplant at the age of 5 years (4).

In the course of the last 4 decades studies tend to demonstrate an early survival advantage by placing a percutaneous shunt between the bladder and the amniotic cavity (VAS) (5). Although VAS is the most common treatment to restore the amniotic fluid volume and alleviate the obstruction, the rate of complications is still very high, 40% (4), and the long term renal function remains uncertain. Anecdotal cases of survival and even good renal function in cases of early bladder decompression are published (6, 7) but prospective series are rare. Survival is improved on the perinatal period, but at 6 months and 2 years follow up there is no evidence of neither a better survival rate nor renal function. Oligohydramnios on the 16–24 weeks of pregnancy can cause irreversible pulmonary hypoplasia (4, 8).

A recent publication by Ruano et al. proposed a new, standardized approach to the selection of patients with LUTO based on multiple criteria including amniotic fluid levels, renal appearance, and fetal urinary electrolyte assessment. The biochemistry and ultrasound characteristics of the fetal kidneys are important to estimate fetal renal function (9).

However, the evaluation of the fetal renal function is difficult since sonographic parameters are not sensible enough and according to some authors biochemical parameters have poor clinical accuracy in the selection of those patients that could benefit from the procedure (10). However, non-favorable results in the biochemistry analysis of the fetal urine correlate with irreversible histological changes in the fetal kidney and aid in identifying fetuses which will not benefit from intervention (11). In a recent publication including 89 patients with prenatally detected posterior urethral valves followed, 20% of the patients were followed for at least 20 years. The authors report that postnatal glomerular filtration rate was $>60$ mL/min/1.73 $m^2$ in 67.4% of the cases and $<30$ mL/min/1.73 $m^2$ in 17%. A combination of β2-microglobulin and chloride had the best prognostic value (93% sensitivity and 71% specificity). They concluded that fetal urine parameters predicted long-term postnatal renal function (12) confirming earlier more preliminary observations (13).

### Posterior Urethral Valves (PUV) Are the Most Common Cause of LUTO

More than one third of the boys with PUV have a lifetime risk for end-stage renal disease (14). Conversely, PUV accounts for 18% of the pediatric end-stage renal disease. In fetal ultrasonography in the second trimester, the keyhole sign (appearance of a distended bladder and prostatic urethra is the most common sign of PUV (1–3).

Urethral atresia (UA) is seen in 0.3/10,000 births. In the absence of spontaneous decompression of the bladder or prenatal intervention, the condition is invariably fatal.

Prune Belly Syndrome (PBS), also known as the triad syndrome or Eagle Barret syndrome in seen in 1/30,000–40,000. The association of PBS with urethral obstruction (which may no longer be present at the time of diagnosis) is no longer disputed (15, 16).

### Prenatal Treatment of LUTO

Prenatal treatment of LUTO dates back more than 3 decades (17). From initial open vesicostomy, treatment have evolved to percutaneous placement of vesicoamniotic shunts to fetoscopic surgery. While open bladder decompression has been abandoned, debate continues regarding the superiority of shunting vs. a fetoscopic approach.

### Vesicoamniotic Shunt (VAS)

In 1986, International Fetal Surgery Registry reported 41% survival after VAS placement (18). With current techniques and patient selection survival is now approaching 70% in the first year (19).

Nassr et al. published meteanalysis which included 9 articles of fetal VAS placement with a follow up to 2 years and better defined diagnosis of LUTO (4). One-hundred-twelve fetuses were shunted and 134 fetuses treated conservatively. Shunted fetuses had statistically better survival in the first 6 months of life (57% VAS vs. 39% observed), but it didn't impact survival between 6 and 12 months. Also there wasn't any evidence that VAS placement improved postnatal renal function. However, it should be noted that the effect of VAS placement was less evident in those patient with better prognosis based on favorable fetal urinary chemistry. In contrast those with poor prognostic features benefitted from VAS placement. Ruano et al. also reported better survival after shunting (8). Historically, Freedman et al. reported series of 55 fetuses with LUTO who received VAS and concluded that: "When evaluated by specific diagnosis, intervention appears to provide outcomes in these high risk fetuses that are comparable to those for disease detected post-natally" (3). A recent meta-analysis also suggests that VAS may improve renal function (20). Unfortunately, until today the rate of complications of VAS reaches almost a 40% including shunt migration, obstruction, and displacement (9).

## Fetal Cystoscopy

Fetal cystoscopy was reported to aid in making an accurate diagnosis at the time of prenatal intervention (21). Cystoscopy permits simultaneous evaluation of the bladder and urethra and even laser ablation of posterior urethral valves (22–25) but after more than 20 years of attempting such treatment the risk of creating fistulas remains high.

In the retrospective study from Ruano et al. (9, 26), 111 fetuses with severe LUTO were evaluated between 1990 and 2013. In 34 fetuses cystoscopy was performed, in 16 VAS was placed and nothing was performed in 16. The overall survival was higher in the group of patients who underwent any kind of treatment; being 43.8% in the VAS group, 38.2% in the fetal cystoscopy group and 19.7% in the group who did not undergo treatment. The 6 months survival rate show no statistically difference between the fetal cystoscopy group and the VAS group. The evaluation of the renal function showed that compared with no treatment fetal cystoscopy significantly improved the renal function, an improvement that could not be demonstrated on the VAS group. After performing multivariate analysis and adjusting for all variables including gestational age at diagnosis of LUTO, type of fetal intervention given, postnatal diagnosis of the cause of LUTO and fetal center location, as well as considering termination of pregnancy, fetal cystoscopy was associated with a significant improvement in the 6 months survival rate and a not significant trend toward normal renal function. Fetal VAS did not show a significant improvement in renal function. Also in this study, complications of those patients undergoing cystoscopy and intervention was high: fistula in 8.8%, and recurrence of LUTO 5.9% which leaded to preterm delivery and death after birth. Complications of VAS, mainly obstruction or migration, occurred in 31.3%.

## Other Urinary Tract Anomalies

In cases of mild upper tract dilatation there is a 11.9% risk of pathological findings, and 1/10 fetuses presenting mild hydronephrosis has a serious condition (27). Ureteroceles may cause bladder outlet obstruction with similar consequences as other cases of LUO. Prenatal detection and fetoscopic treatment has been reported (28, 29).

Thus, prenatal intervention in LUTO improves survival in the worst cases by improving pulmonary function and it may be advantageous for renal function, particularly in patients with adverse urine parameters.

## Hydrocolpos and Cloaca

A retrovesical cystic mass in a female fetus usually represent a Mullerian structure filled with fluid. Mallman et al. reported 20 cases which illustrate the spectrum of differential diagnoses, associated malformations and possible course of action (30). Most of the cases were detected in the late ultrasound screening, and only one in the second semester screening (median gestational age at diagnosis 30 weeks). Intra-abdominal cystic masses present a difficult differential diagnosis which may include hydronephrosis, fetal ovarian cysts, anterior cystic teratoma, cloacal malformation, intra-abdominal teratoma, anterior meningocele, and hydrocolpos. Most of the fetuses presenting hydrocolpos will prove to have a severe malformation. Final diagnoses in this series included anorectal malformation in 13, anal atresia, cloacal malformation, cloacal exstrophy intra-abdominal teratoma, vaginal atresia or duplication, persistent urogenital sinus or cardiac malformations. Two of twenty parents opted for termination of pregnancy, three suffered intrauterine fetal death. Fifteen were born at median gestational age of 35 weeks and underwent postnatal reconstructive procedures. Of interest is that the association with ascites indicated a severe associated malformation such as a cloacal malformation (31). Persistent urogenital sinus with hydrometrocolpos is a potentially treatable malformation but the fetal survival depends on the other associated anomalies and the time of prenatal diagnosis. Prenatal decompression may be used in selected cases (32).

Prenatal detection of hydrometrocolpos rarely leads to prenatal intervention but allows improved family counseling.

## Congenital Adrenal Hyperplasia (CAH)

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is an autosomal recessive disorder caused by mutations in the CYP21A2 gene. The incidence of the classic form varies between 1/15,000 and 1/24,000, more common in Asians and Caucasians than in Africans. In the classic form synthesis of cortisol and aldosterone are impaired which may result in adrenal insufficiency and salt wasting and in females, virilized genitalia (33).

Genetic studies reveal a mutation in the CYP21A2 gene. Although numerous mutations have been reported, 10 are found in the majority of cases. Prenatal genetic studies allow early detection of the mutation in subsequent pregnancies.

Prenatal diagnosis is recommended in pregnancies when both parents are carriers of the disorder, one parent has a clinical manifestations of CAH or there an affected family member (34). German guidelines recommend prenatal diagnosis in the following cases: (1) Families with one affected child (index case) with classic CAH (CYP21A2); (2) Known parental heterozygosity for classic CAH (no index case) (3) New relationship of a parent of a child with classic CAH if the new partner is known to be a carrier for classic CAH; (4) Homozygosity or compound heterozygosity for classic CAH of one parent when the other parent is a heterozygous gene carrier for classic CAH (35).

As recently as 2015 prenatal treatment of fetuses at risk of virilization was considered experimental in Germany. Part of the reason for this reservation was that for the treatment with dexamethasone to be effective, it had to be initiated before the diagnosis could be confirmed by chorionic villous sampling which expose non-affected fetuses to unnecessary treatment. New developments in the diagnosis by non-invasive methods performing genetic testing of fetal DNA extracted from maternal blood might make the treatment more acceptable (36).

The aim of the prenatal treatment is to avoid virilization of the female fetus. The treatment with dexamethasone was introduced in 1978 by Forest in France and in 1986 in the U.S. Although highly effective if used consistently before the 8 week of those pregnancies at risk, it is not absent of controversies due to animal studies showing effects on brain

development (37) but the issue remains controversial (38). With older invasive diagnostic methods (chorionic villus sampling), the sex of the child is determined between 12th and 14th weeks, treatment is suspended if the child is a male or a non-affected female which meant unnecessarily treating 7 of 8 fetuses (37). Non-invasive DNA analysis may overcome these objections (36, 39).

Nevertheless, other potential adverse effects on the cardiovascular, renal and metabolic functions are likely but not yet well-understood (40).

Prenatal treatment of female fetuses at risk of having CAH reduces virilization. Non-invasive fetal DNA analysis allow earlier diagnosis, reducing the risk of treating with dexamethasone males and non-affected fetuses.

### Myelomeningocele

Myelomeningocele (MMC) is a life altering birth defect, which results from an incomplete closure of the neural tube during the fourth week of gestation. It affects 5 of 10,000 births (41). Prenatal closure of the myelomeningocele aims at reducing the noxious effect of the amniotic fluid on the exposed spinal cord (42). Fetal repair of has been done by open surgery, fetoscopic surgery, or a combination of both.

The MOMS trial (43) was a multicenter study comprising 183 fetuses of which 158 were evaluated at 12 month of age that demonstrated that, within the period of the follow-up the incidence of ventriculo-peritoneal shunt placement were reduced from 82% in the group operated after birth to 40% in the prenatally operated group. Other potential benefits of prenatal closure included better mental development and motor function. Disadvantages of fetal closure included an increased risk of preterm delivery and uterine rupture at delivery.

Since first MMC closure 1998 (44), nine reports of urological outcomes on 291 cases have been published worldwide (45–52). Most reports that compared early bladder function of MMC patients treated pre- or post-natally failed to show nay advantages. However, there are two encouraging reports. Carr, based on interviews with 54 patients or families who had prenatal closure of MMC, reported that 10 children (18.5%) were toilet-trained, two patients had stool continence, and one was continent of urine but required bowel management, suggesting better outcomes than expected with postnatal closure (53).

Horst et al. reported urodynamic outcomes in 8 of 30 children with 2 year follow-up whose MMC was closed prenatally and compared them with a group with conventional treatment (51). Although they report that bladder function was normal in half of the patients. However, given the difficulties of evaluating bladder function before toilet training the results must be interpreted with caution. Bladder wall thickness was significantly more frequent in prenatally treated patients. This may be the result of better neurological outcome or sphincter denervation as reported by others (47).

Fetal treatment of MMC is gaining momentum. Prospective studies including standardized urologic evaluation will determine if the encouraging results reported by some hold on the long term follow-up.

## CONCLUSIONS

1. Prenatal intervention in LUTO improves survival in the worst cases by improving pulmonary function and it may be advantageous for renal function, particularly in patients with adverse urine parameters. Development of better instrumentation would improve the success of fetal cystoscopy and reduce complications.
2. Prenatal treatment of female fetuses at risk of having CAH reduces virilization. Non-invasive fetal DNA analysis allow earlier diagnosis, reducing the risk of treating with dexamethasone males and non-affected fetuses.
3. Fetal treatment of MMC is gaining momentum. Prospective studies including standardized urologic evaluation will determine if the encouraging results reported by some hold on the long term follow-up.

## AUTHOR CONTRIBUTIONS

All authors contributed to the conception of this review. BB and RG conducted the review of the literature and wrote the manuscript. AL and BL contributed substantially to the preparation of the manuscript.

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REVIEW
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# Diagnosis and Management of Bladder Dysfunction in Neurologically Normal Children

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Normal bladder and urethral sphincter development as well as neural/volitional control over bladder-sphincter function are essential steps for regular lower urinary tract function. These maturational sequences are clinically evident by the age of 5 years. However, in 17–22% of children, symptoms persist beyond that age, characterizing lower urinary tract dysfunction (LUTD). The clinical spectrum is wide and includes overactive bladder, voiding postponement, underactive bladder, infrequent voiding, extraordinary daytime only urinary frequency, vaginal reflux, bladder neck dysfunction, and giggle incontinence. LUTD may lead to vesicoureteral reflux and recurrent urinary tract infections, increasing the likelihood of renal scarring. LUTD is often associated with constipation and emotional/behavioral disorders such as anxiety, depression, aggressiveness, and social isolation, making diagnosis, and treatment imperative. Diagnosis of LUTD is essentially based on clinical history, investigation of bladder storage, voiding symptoms (urinary frequency, daytime incontinence, enuresis, urgency) and constipation. Dysfunctional Voiding Score System (DVSS) is a helpful tool. Physical examination focuses on the abdomen to investigate a distended bladder or palpable fecal mass, the lumbosacral spine, and reflex testing. Bladder diaries are important for recording urinary frequency and water balance, while uroflowmetry is used to assess voided volume, maximum flow, and curve patterns. Bladder ultrasonography to measure post-void residual urine volume and urodynamics are used as supplemental tests. Current first line treatment is urotherapy, a combination of behavioral measures to avoid postponing micturition, and a restricted diet for at least 2 months. Anticholinergics, β3 agonists and neuromodulation are alternative therapies to manage refractory overactive bladder. Cure rates, at around 40%, are considered satisfactory, with daytime symptoms improving in 32% of cases. Furthermore, children who are also constipated need treatment, preferentially with polyethylene glycol at doses of 1–1.5 g/kg in the 1st 3 days and 0.25–0.5 g/kg thereafter until the 2-month period of behavioral therapy is complete. If urotherapy fails in cases of dysfunctional voiding, the next step is biofeedback to teach the child how to relax the external urethral sphincter during micturition. Success rate is around 80%. Children with underactive bladder usually need a combination of clean intermittent catheterization, alpha-blockers, biofeedback and neuromodulation; however, cure rates are uncertain.

**Keywords: incontinence, lower urinary tract dysfunction, overactive bladder, children, constipation, electrical nerve stimulation, neuromodulation**

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## INTRODUCTION

The physiological function of the bladder and lower urinary tract develops as children grow. Socially acceptable conditions are achieved progressively, with voiding control being reached at around 5 years of age. When lower urinary tract symptoms (LUTS) persist beyond that age, the condition is referred to as lower urinary tract dysfunction (LUTD). This condition has been reported to affect 17–22% of children (1–3).

Children with LUTD are more likely to develop urinary disorders such as vesicoureteral reflux and recurrent urinary tract infection (UTI). These conditions increase the likelihood of renal scarring (4), which, over the long term, may progress to kidney failure (5–7). Children and adolescents with LUTD may also express emotional and behavioral disorders such as anxiety, depression, aggressiveness, and social isolation. It's unknown which one is the cause and the consequence (8); the pathological condition underlying this association is a complex problem. In a trial, 29.4% of patients with LUTD were diagnosed with concomitant psychiatric disorders, mainly attention deficient hyperactivity disorder (8). In addition, they run an increased risk of experiencing bullying (4, 9).

LUTD may be associated with other conditions, the most common being constipation. Children with constipation have been reported to be 6.8 times more likely to have LUTD compared to children with normal bowel function (10). A probable explanation for this phenomenon is that the bowel and bladder share afferent nerves, similar neural centers, and a common embryological origin. When constipation and LUTD are both present, the condition is referred to as bladder and bowel dysfunction (BBD) (11).

The term LUTD refers to different clinical characteristics depending on the physiopathology and symptomatology involved. According to the International Children's Continence Society (ICCS), LUTD encompasses the following range of symptoms: overactive bladder (OAB), voiding postponement, underactive bladder, infrequent voiding, extraordinary daytime only urinary frequency (EDOUF), vaginal reflux, bladder neck dysfunction, and giggle incontinence.

This review article dedicates to describe the diagnosis and treatment of LUTD according to the most recent publications.

## DIAGNOSIS

Diagnosis of LUTD is essentially based on clinical history, physical examination, bladder diary (BD), symptoms score such as the Dysfunctional Voiding Score System (DVSS), associated with uroflowmetry and bladder ultrasonography to measure post-void residual urine volume (**Figure 1**).

### Clinical History

The diagnosis of LUTD is essentially based on a thorough evaluation of the patient's clinical history. Anamnesis will focus on the patient's medical and surgical history (12), including any previous medications used to treat the current pathology and any other non-pharmacological treatments such as behavioral therapy or physiotherapy. Bladder storage, voiding symptoms and constipation should be investigated (6, 13). Urinary frequency, hesitancy, daytime incontinence, enuresis, urgency, urge incontinence, pelvic pain, and urine flow patterns are also relevant. None of these symptoms is expected to be present in children over 5 years of age; otherwise, the child should be managed as having LUTD.

To avoid involuntary urine loss, children often perform holding maneuvers. In girls, these usually consist of crossing their legs, with one knee over the other, pressing their genitals, walking on tiptoe and squatting. It has been reported that 73% of children with LUTD perform holding maneuvers (14).

The presence of constipation is evaluated based on reported symptoms such as excessive straining during defecation, hard stools, a feeling of incomplete evacuation or anorectal blockage, the use of manual evacuation maneuvers to facilitate defecation or the occurrence of fewer than three spontaneous evacuations per week (10). Patients will be asked about the characteristics of their stools. Recognizing BBD is crucial, since constipation needs to be treated together with voiding issues. Treating this disorder usually reduces urinary symptoms and decreases the likelihood of developing a UTI (15, 16).

Mothers of children with LUTD have also been shown to be more likely to have voiding symptoms. If constipation is included, this likelihood is even greater (17).

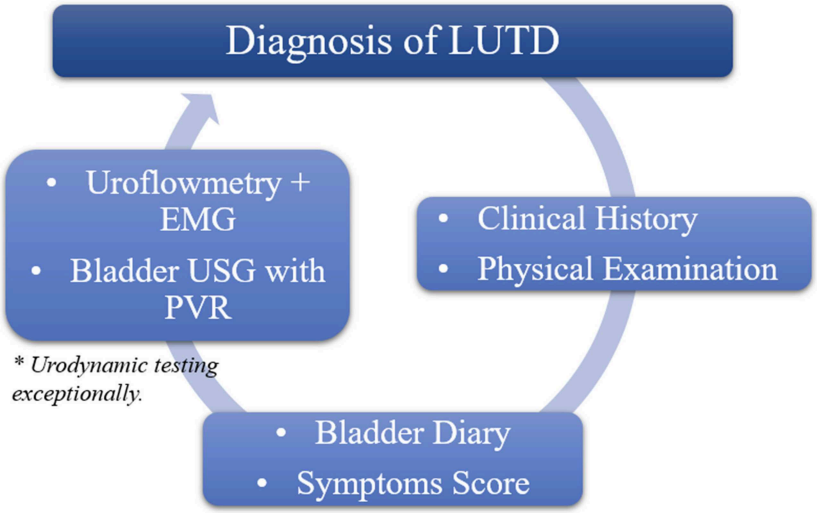
Furthermore, questions should be asked regarding the child's psychological development, particularly with respect to stressful events that may have occurred in the life of these children, the presence of anxiety, excessive shyness, aggressiveness, oppositional behavior, attention deficit/hyperactivity disorder, etc. (8). If an emotional disorder is suspected, the child should be referred for psychological evaluation (8).

### Physical Examination

Physical examination focuses on the possibility of a distended bladder and the presence of a palpable fecal mass in the abdomen or possible fecal impaction in the rectal ampulla (18). In this clinic, rectal examination is not routinely performed so as to avoid causing discomfort to the children. A complete examination of the lumbosacral spine is performed to investigate for defects suggestive of spina bifida and the cremasteric and anal sphincter reflexes are tested (18).

### Bladder Diary (BD)

The bladder diary is used to record urine output and frequency as well as fluid intake and any occurrence of urgency or involuntary urine loss. Recently, a bladder diary maintained over two, not necessarily consecutive, days has been shown to provide data that are similar to those obtained over a 3-day period (19). The color of the urine is also routinely evaluated to assess the patient's state of hydration. A possible bias must be considered, on account of BD use may lead to a bladder training effect and nights during recording have evidenced relevant variations in the frequency of nocturnal voids. Despite that, it continues to be one of the most important and simplest tools to access LUTS, setting more confidence to the diagnosis commonly overestimated by DVSS (20).




EMG: electromyography. USG: ultrassonography. PVR: post-void residual urine volume.

**FIGURE 1 |** Illustration showing a representation of diagnostic tools for LUTD.

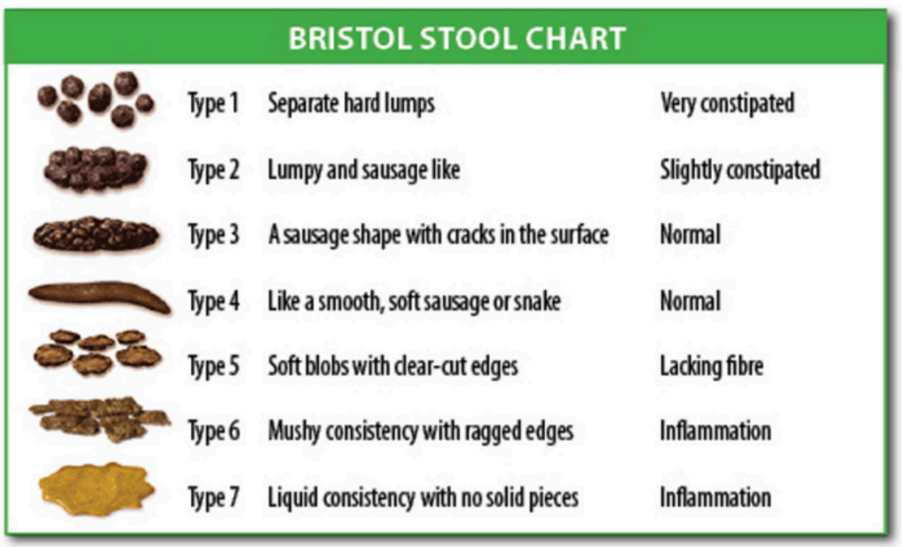



**FIGURE 2 |** Illustration showing the Bristol Stool Chart. (Source: The Organic Dietitian). Source: Wikipedia Commons. Bristol Stool Scale. [online publication] Salvador, 2019. Wikipedia Commons October 22, 2015 (accessed on July 2, 2019). Available at: https://commons.wikimedia.org/wiki/File:Bristol_stool_chart.svg.

## Symptoms Score

Specific questionnaires have been developed for use in the investigation of LUTS, including the Dysfunctional Voiding Score System (DVSS), the Dysfunctional Voiding and Incontinence Score System (DVISS), and the Incontinence Symptoms Index-Pediatric (ISI-P) (6). These scores have little relevance in clinical practice; however, they are important tools in clinical investigation, particularly with respect to standardizing the terms used and as a guide for professionals with less experience. They are complementary tools to BD, in order to evaluate not only the actual voiding but also the self-reported behavior, a direct reflection of how LUTD impacts (20).

Due to the significant association between constipation and LUTD, this condition should also be assessed through the use of questionnaires such as the Rome IV diagnostic criteria and the Bristol stool scale (**Figure 2**). We believe these scores to be extremely important, since this pathology may fail to be diagnosed if incorrectly evaluated.

### Biomarkers

Nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) are messengers emitted from the uroepithelial bladder smooth muscle aiming to differentiate neuronal cell in peripheral nervous system. These biomarkers are believed to be increased in the urine of patients with OAB (21). Studies have already observed decreased urine levels during treatment as well as an increase after quitting the treatment, inciting questions about the biomarker's real role in the pathophysiology. So far, results show they could not predict who would benefit from the treatment with antimuscarinics, but more robust studies are yet in course (21).

## NON-INVASIVE ADDITIONAL EVALUATION

Our group has previously shown that, although clinical history is sufficient to enable a diagnosis of LUTD to be reached, it is not that specific for the identification of abnormalities in the emptying phase, such as dysfunctional voiding (22). Therefore, once the patient's clinical history has been thoroughly investigated, additional examinations may prove necessary. Urinalysis is one of the tests available, together with urine culture if a UTI is suspected. Samples for urinalysis are simple to collect, and in certain cases, can guide the investigation toward specific urinary tract pathologies (22).

### Uroflowmetry

Uroflowmetry is an indispensable test for children with LUTD. Simple to perform, non-invasive and fast, this test provides important data such as: voided volume, voiding time, maximum flow, curve pattern, and rate of flow. Uroflowmetry results showing a voided volume of at least 50 ml or 50% of the expected bladder capacity for age [(age in years + 1) × 30] are considered adequate (23, 24).

Uroflowmetry provides relevant data on lower urinary tract (LUT) function and on the possible etiology of LUTD. The type of curve pattern identified at uroflowmetry may suggest specific conditions. A bell-shaped curve is considered physiological. Conversely, a staccato-shaped pattern suggests dysfunctional voiding or bladder and bladder neck dysfunction, while a tower-shaped curve is indicative of OAB, a plateau is suggestive of a LUT obstruction and an interrupted curve is typical of an underactive bladder. Interpreting uroflowmetry curves can be subjective and conclusions may vary from one professional to another (23, 24).

The flow index (FI) is a new parameter that is now available and is reached by dividing the actual Qmax by the estimated Qmax. In boys, an FI $< 0.70$, is indicative of a flat curve, while an FI of 0.71 to 1.25 suggests a bell-shaped curve, and values $> 1.25$ are typical of a tower-shaped curve. In girls, an FI $< 0.68$ strongly implies a flat curve, while values of 0.69 to 1.1 suggest a bell-shaped curve, and values $> 1.1$ suggest a tower-shaped curve (23, 24).

Uroflowmetry with electromyography (uroflow-EMG) is a non-invasive evaluation method that provides information on the functionality of the pelvic floor and external sphincter. The procedure consists of attaching electrodes in the perineal area at the 3 and 9 o'clock positions. Simultaneous use of electromyography during uroflowmetry adds relevant data during micturition, including coordination or lack of coordination in the relaxation of the sphincter. In addition, this method provides the lag time, i.e., the time required for the pelvic floor to relax once micturition is initiated, which should be between 2 and 6 seconds. The concept that the time the pelvic floor takes to relax immediately prior to detrusor contraction and the beginning of voiding is longer in patients with dysfunctional voiding is widely accepted (25). No pelvic floor activity is expected during voiding in patients with genuine OAB. Conversely, patients with dysfunctional voiding will have a tonic contraction of the sphincter during voiding (sharp peaks on the EMG) (26). This method is susceptible to artifacts, and the electromyographic activity does not always reveal sphincter activity. The effectiveness of electromyography for tower-shaped and bell-shaped curves has yet to be clarified (27).

### Bladder Ultrasonography and the Measurement of Post-Void Residual Urine Volume

For reliable data to be obtained, bladder volume should be between 50 and 115% of the expected capacity for age. In addition, post-void residual urine volume should be measured in the 1st 5 min after micturition and, in ideal conditions, $<1$ min after micturition. Post-void residual urine volume $<20$ ml on more than one occasion is considered abnormal (**Figure 3**) (28). Bladder wall thickness, measured on an empty bladder, should be $<3$ mm. In constipated children, measuring the rectal diameter is also helpful, with measurements $>3$ cm being considered clinically significant. Dynamic bladder ultrasonography has been reported as being useful in evaluating pelvic floor contraction when involuntary contractions are present in cases of OAB. However, the clinical relevance of these findings has yet to be established (29).

### Urodynamic Testing

Urodynamic testing in children with LUTD and no neurological abnormalities is only recommended when treatment has persistently failed, in cases of underactive bladder, or when there is significant bilateral dilation of the upper urinary tract. In this situation, video urodynamics is a useful tool with which to identify vesicoureteral reflux and differentiate between bladder neck and bladder sphincter discoordination (28).

## CLASSIFICATION (ICCS)

### OAB

The presence of urinary urgency is usually associated with daytime urinary incontinence and frequency.

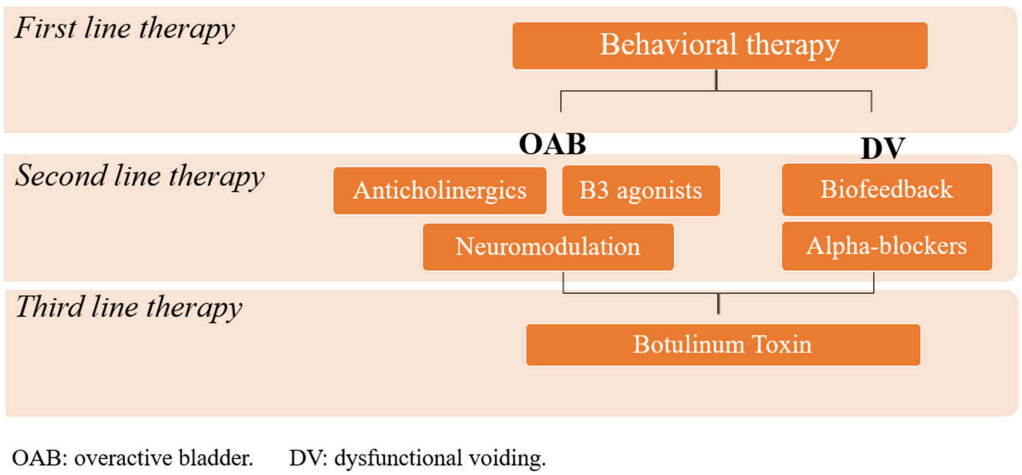
### Voiding Postponement

Low daytime micturition frequency ($\leq 3$ times/day), but with no post-void residual urine. In such cases, the child usually performs holding maneuvers to postpone voiding.

| DEFINITIONS<br>INTERNATIONAL CHILDREN'S CONTINENCE SOCIETY | |
|---|---|
| Decreased Daytime Voiding Frequency | </=3 voidings/day |
| Increased Daytime Voiding Frequency | >/=8 voidings/day |
| Polyuria | <2 liters/m² of BSA – 24hrs<br><5ml/kg/hr |
| Expected Bladder Capacity | [(age in years + 1)] x 30] ml |
| Residual Urine | Excess of 5-20ml indicates incomplete bladder emptying |

BSA: body surface area

**FIGURE 3 |** Illustration showing the International Children's Continence Society (ICCS) definitions.




OAB: overactive bladder. DV: dysfunctional voiding.

**FIGURE 4 |** Illustration showing an schematic representation of lines of treatment of LUTD.

## Dysfunctional Voiding

Discordant bladder and perineal activity, with or without post-void residual urine. The child may fail to relax the bladder neck during micturition.

## Underactive Bladder

Low voiding frequency during the day ($\leq$ 3 times/day) associated with a large amount of post-void residual urine. Detrusor function is abnormal at urodynamic testing. This is the only situation in which urodynamic testing is normally recommended as part of the initial workup.

## Giggle Incontinence

Incontinence when the child laughs.

## Vaginal Reflux

This occurs due to the position adopted by some girls, particularly overweight girls, while voiding. As the girl gets up, urine dribbles from the vagina.

## EDOUF

A sudden increase in daytime voiding frequency unrelated to either urgency or incontinence. Generally associated with anxiety and stressful events.

All these conditions are frequently intertwined. For instance, children with dysfunctional voiding often have symptoms of OAB.

# TREATMENT

First line therapy is aimed at improving voiding habits in children with LUTD (**Figure 4**).

## Behavioral Therapy (Urotherapy)

This form of treatment consists of training children and adolescents to void every 3 h and whenever they feel the need to urinate or when they perform holding maneuvers. They are instructed to ensure that their fluid intake during the day is adequate and to restrict their consumption of caffeine, chocolate

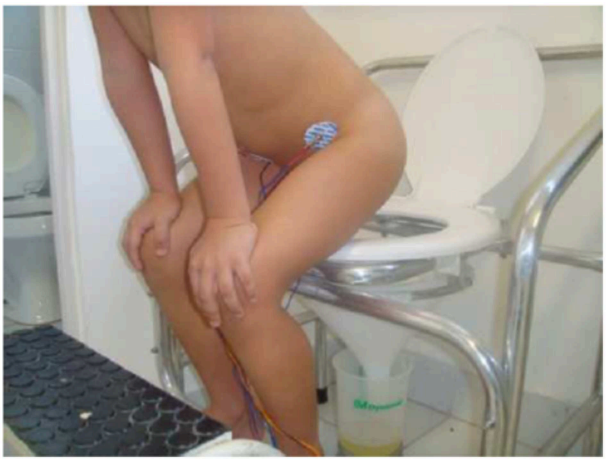


**FIGURE 5 |** Illustration showing a wrong voiding posture, using pelvic floor muscles. Written informed consent was obtained from this patient and his/her legal guardians authorizing publication of this image.

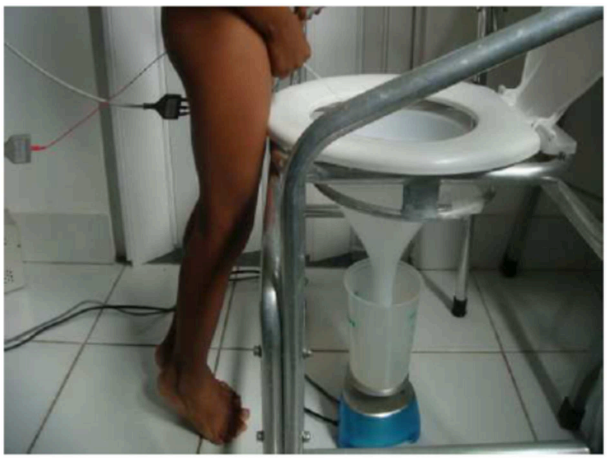


**FIGURE 6 |** Illustration demonstrantes another incorrect voiding posture. The tip toe position activates pelvic floor muscles. Written informed consent was obtained from this patient and his/her legal guardians authorizing publication of this image.

and citrus fruits. The position adopted during micturition and defecation also merits attention. Both feet should be resting on a flat surface and the coordination between the relaxation of the pelvic muscle and the bladder contraction should be closely observed (**Figures 5**, **6**) (30). Urotherapy must be continued for at least 2 months, with reevaluation required at the end of this period. Nowadays, there are mobile applications aimed at helping patients during behavioral therapy. Furthermore, for children who are also constipated, treatment with polyethylene glycol should be initiated, at doses ranging from 1 to 1.5 g/kg in the 1st 3 days and 0.25–0.5 g/kg thereafter until the 2-month period of behavioral therapy is complete (4).

This modality of treatment works better for patients who tend to postpone voiding, with cure rates of around 40% and an improvement rate of 32% in daytime symptoms (31).

Once this initial line of treatment is complete, if symptoms persist, individualized management is required, with the type of treatment depending on the kind of dysfunctional voiding present. For those with genuine OAB in whom initial behavioral therapy failed, anticholinergics are the first line of choice for pharmacological therapy (32), and neuromodulation (transcutaneous parasacral or posterior tibial nerve stimulation) is the best non-pharmacological option (14). However, OAB often presents in association with other types of LUTD, such as voiding postponement and dysfunctional voiding. The approaches used and the different forms of management for each case are described and discussed below.

## Second Line and Additional Therapies

When urotherapy fails, other forms of treatment are required. Different treatment options should be considered for the different conditions.

## OAB

OAB can be managed either by medication, by neuromodulation, or by a combination of both.

### Anticholinergics and β3 Agonists

These drugs are better suited for the treatment of genuine OAB, when patients do not postpone micturition and void correctly. Antimuscarinics are widely used; however, treatment is often discontinued due to a lack of effect or bothersome side effects. These drugs act by antagonizing the response to acetylcholine and other parasympathomimetic substances that are mediated through activation of the muscarinic receptors (principally M2 and M3) in the bladder (33). The beta-3 agonist, mirabegron, was introduced in 2012 as a new drug for the treatment of OAB (33).

In one analysis, oxybutynin, and solifenacin were found to be the most cost-effective antimuscarinics (34).

Oxybutynin is the most commonly prescribed anticholinergic. The recommended dosage is 0.2 to 0.6 mg/kg (with a maximum dose of 15 mg/day) and its effectiveness has been reported as around 30–40% (35). Although oxybutynin has been the most commonly prescribed medication for OAB in children for years, no randomized clinical trial has yet been conducted to compare this drug with placebo. Tolterodine, available in tablets of 1 and 2 mg, can also be used for the treatment of OAB. In one systematic review, the dose of tolterodine used in trials ranged from 0.8 to 8 mg/day (1). Overall, the success rate was comparable to that of oxybutynin (1). A randomized clinical trial compared tolterodine and placebo and failed to show any difference in outcome between the groups (2).

The antimuscarinic solifenacin has a long half-life. Although still off label, the drug has been used at a dose of 5 mg once a day. One study reported a complete response rate of 53% (3). In another prospective multicenter study, treatment with

solifenacin resulted in improvement, as shown by the difference in maximum voided volume between baseline and the end of treatment, and in a decrease in voiding frequency (4). However, in one randomized clinical trial the rate of resolution of LUTS with solifenacin was similar to that found with placebo (5). In patients with refractory OAB, combination therapy is an option in more refractory cases. However, treatment with the combined medication was discontinued in 22% of patients due to adverse events and in 54% due to a lack of efficacy (36).

The side effects of antimuscarinics include constipation, dry mouth, heat intolerance and, more rarely, mental confusion increasing the discontinuation rate with oxybutynin to 32% (37). The prevalence of these side effects has been described as follows: of the 53% of patients who reported a side effect, 29% reported dry mouth, 19% pruritus, 8% vertigo, 8% constipation, 6% headache, and 2% another side effect (37).

Mirabegron is a selective beta-3 adrenoceptor agonist with a different pharmacologic profile and mechanism of action to those of antimuscarinics. Bladder relaxation is obtained through activation of the beta-3 adrenoceptor and the subsequent activation of adenylyl cyclase (36). In adults, Mirabegron has been shown to be effective for the treatment of OAB, with few side effects; however, it is off label for children (38). One study reported a complete response rate in 22% of 58 children, and almost all the patients experienced some improvement in the severity of the symptoms of incontinence (6). In one study, mirabegron, and solifenacin were both shown to improve OAB symptoms, with no statistically significant difference between the two treatments. Both drugs were well-tolerated (38). Combination treatment with antimuscarinics and mirabegron may represent a promising option for patients who fail to respond to monotherapy (39). Although, the aim of the investigation is still to deduce how durable the effect of Mirabegron is in successfully-treated overactive bladder patients. A multicenter study involving adult and elderly participants concluded that most patients who discontinued treatment (69%) could only do so temporarily, considering a worsening of symptoms rapidly occurred, in an average of 48 days (increased number of frequency, urgency, and nycturia) (40).

In summary, anticholinergics may prove effective for children with OAB (35). Some randomized clinical trials have failed to find any difference between these medications and placebo, probably because of the high effectiveness of urotherapy in those studies (35–37). This means that the sample studied consisted of patients with voiding postponement plus OAB, which is the condition that responds best to behavioral therapy. The most common problems with antimuscarinics are the high rate of side effects (including the possibility of these drugs crossing the blood-brain barrier, thus causing mental confusion), the fact that constipation may worsen, and that treatment time is unknown (37).

## Neuromodulation

There are different modalities of neuromodulation that can be useful for the treatment of OAB, including parasacral transcutaneous electrical nerve stimulation (TENS), posterior tibial nerve stimulation (PTNS) and sacral implants (41).

Parasacral TENS has traditionally been performed with electrodes placed bilaterally in the region of S3, with different energy parameters and periodicity. The usual current frequency is 10 HZ (41). Pulse widths have varied from 100 to 700 microseconds (42). The intensity of the current is increased according to the patient's tolerance level.

With parasacral TENS, there is complete resolution of the symptoms of OAB in 63% to 73% of cases (43). The outcome with this treatment proved better than with sham in two randomized clinical trials (44, 45). One study reported a higher success rate for TENS + urotherapy compared to urotherapy alone (67 vs. 43%) in children with OAB who had failed to respond to previous treatments; however, the difference was not statistically significant, perhaps because the sample was underpowered for this evaluation, since the success rate with urotherapy is high. However, for patients who had undergone no previous treatment, the success rate was 71% in the TENS + urotherapy group and 48% in the urotherapy alone group ($p = 0.05$). In a study conducted by our research group, the cure rate with TENS for cases of OAB in children was 73%, with a recurrence rate of 10% over a follow-up period of at least 2 years (8).

TENS was compared with oxybutynin in a randomized clinical trial and the outcome was shown to be similar insofar as the improvement of symptoms was concerned. However, about half the patients randomized to oxybutynin experienced side effects directly related to the drug. Moreover, only those randomized to TENS experienced an improvement in constipation, which was achieved in 85% of cases (10, 11). The ability to manage BBD with just one treatment is another advantage of TENS (11).

When first described in children, the use of PTNS was shown to result in an improvement in 50% of the children with OAB, with 35% of the symptoms being completely resolved (12). Our group conducted a comparative study in which cure was achieved in 70% of children with OAB in the sacral TENS group compared to 9% in the PTNS group (46). It is possible that the distance from the posterior tibial nerve to S3 may be responsible for this difference in effectiveness (46).

With the idea of removing the impedance of the skin and getting closer to the S3 innervation, a new form of treatment was developed that consists of placing acupuncture needles at S3 (**Figure 7**). Sessions are performed once a week using the same electrical parameters established for parasacral TENS. In our pilot study of 17 cases, complete response to treatment was achieved in around 70% of cases, with minimal discomfort (46). Further studies are needed to test the efficacy of this method.

Sacral nerve modulation with an implantable pulse generator, i.e., the use of implantable sacral nerve stimulators, is currently undergoing evaluation in patients under 18 years of age. Groen et al. (47) reported an improvement in symptoms in 50% of treated children with OAB, all of whom were refractory to conventional pharmacological treatment (44). In another study, sacral nerve stimulation was found to improve the quality of life of children with LUTD (48).

In patients diagnosed with refractory overactive bladder, and especially those who do not wish to undergo invasive reconstruction surgery, the intravesical injection of Botulinum toxin A constitutes an innovative resource. The neurotoxin inhibits acetylcholine and adenosine triphosphate release from

**FIGURE 7 |** Illustration showing a child undergoing transcutaneous electrical nerve stimulation. Written informed consent was obtained from this patient and his/her legal guardians authorizing publication of this image.

parasympathetic presynaptic nerve terminals, causing flaccid muscle paralysis. Previous trials evidence a complete response rate of 32–60% during a 6-month follow-up, and 44% of children were entirely dry at the end of 12 months (49). Studies conducted on adults found that the intravesical injections increased the risk of urinary retention by nine times. Nonetheless, this problem was minimally registered on pediatric population, and usually reversible (49). Many aspects of the technique are yet to be standardized, though. There is no data on whether to preserve trigon region or not during the injection, the number of injections varies widely, between 12 and 40, as well as the depth, since there isn't proof suggesting whether suburothelial injection is better than the intradetrusor or not (49).

## DYSFUNCTIONAL VOIDING

In cases of dysfunctional voiding, treatment is aimed at improving sphincter relaxation during micturition. Therefore, when urotherapy alone fails, the next step is biofeedback. The objective of this treatment is to teach the children how to relax the external urethral sphincter during micturition. The success rate with this procedure is around 80% (50, 51). Biofeedback sessions usually last 40 min and are performed once a week. Animated biofeedback helps children interact more with the treatment but does not change the final outcome. Patient or family motivation is essential in order to improve compliance. Children over 5 years of age engage better with biofeedback (41, 50).

When bladder neck dysfunction is suspected, alpha-blockers can be an option, although a randomized clinical trial with an admittedly small sample size failed to confirm the effectiveness of this treatment (52). Indications for alpha-blockers include a long EMG lag time at uroflowmetry, bladder neck dysfunction as shown at video urodynamics, and dysfunctional voiding patients who fail to respond to biofeedback to improve bladder neck relaxation (53). A few small studies have also reported good results in some patients using alpha-blockers combined with biofeedback to improve post-void residual urine (52, 54). The dose used is normally Doxazosin 1–2 mg daily (54).

For cases in which all treatments for dysfunctional voiding have failed, an external urethral sphincter injection of botulinum toxin may be an option. The usual doses range from 50 to 100 UI. This form of treatment normally results in improved post-void residual urine volume and urine flow 1 to 2 weeks after the injection. There is a possibility, however, that incontinence could develop secondary to the injection, with this usually resolving itself within 6 months of the procedure (15, 55). Moreover, the effectiveness of botulinum toxin for dysfunctional voiding has yet to be established.

Neuromodulation has also been used for dysfunctional voiding. Capitanucci et al. (55) reported that symptoms resolved completely with this method in around 85% of patients. Our group showed that this method can be used as salvage therapy for patients with dysfunctional voiding and OAB symptoms who fail to respond to biofeedback (56–58). According to the ICCS guidelines, antimuscarinics are indicated for patients with OAB symptoms and dysfunctional voiding who fail to respond to urotherapy. Nevertheless, although few studies have been published in the literature on this subject, in our view the bladder capacity of these patients tends to be large and they are likely to be constipated (13). Therefore, these patients are not good candidates for anticholinergics, since those drugs will increase bladder capacity even further and can worsen constipation (11).

## UNDERACTIVE BLADDER

There are no drugs currently on the market for the treatment of underactive bladder and a combination of measures is generally required. These measures include clean intermittent catheterization, alpha-blockers, biofeedback, and TENS. The therapeutic response to these measures, however, is uncertain. The implantation of sacral nerve modulators has been investigated (57, 59, 60); however, further studies are required.

## ANTIMICROBIAL PROPHYLAXIS FOR URINARY TRACT INFECTIONS

Continuous antimicrobial prophylaxis is generally recommended for children with vesicoureteral reflux, and according to large trials (RIVUR), and it is associated with a 2-fold reduction in risk to prevent recurrent urinary tract infections (61). Despite that, this practice has been questioned lately. Studies have noted that, since it requires regular therapeutic adherence, and it varies from 40–90% in this population, the risk of future renal scarring may not reduce. Plus, there are side effects of antibiotic exposure, remaining only the doubt as to whether this longstanding strategy is actually effective (61).

## PSYCHIATRIC DISORDERS

The interest in the association between psychiatric disorders and LUTD has been growing and generating and is an important field of research. Studies show that children with improvement in psychiatric disorders also had an improvement in their LUTD treatment compliance and a better overall outcome, but also that the treatment of voiding disorders may improve the psychiatric issues that originally required care (8). Therefore, it seems to be a good practice to apply a screening test for psychological problems and, if needed, refer these patients to appropriate care (8).

## CONCLUSIONS

In conclusion, neurologically normal children may present with symptoms of the lower urinary tract, which must be recognized in a timely manner by pediatricians so that treatment can be initiated as early as possible. With the multiple treatment modalities currently available, high cure rates can be achieved.

## AUTHOR CONTRIBUTIONS

All three authors have made substantial contribution to the project, participating of all phases. MF wrote the first version, complemented by the work of JM. UB revised and performed modifications, lapidating the final work.

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frontiers in Pediatrics

REVIEW
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# Surgical Management of Neurogenic Sphincter Incompetence in Children

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We report on the results of a literature review regarding the indications and results of operations to increase bladder outlet resistance to achieve dryness in children with neurogenic sphincter incompetence (NSBD). The relative advantages and disadvantages of injection of bulking agents, periurethral slings, bladder neck reconfiguration, artificial sphincters, and bladder neck closure based on a literature review and our combined clinical experience are discussed. Based on this review and our experience, we propose that periurethral injection of bulking agents is not justified as a primary treatment. Likewise, operations that reconfigure the bladder neck are not very useful since most patients also require bladder augmentation and an abdominal catheterizable channel. Bladder neck slings with autologous tissues are effective, mostly in females bur in the majority of patients a bladder augmentation is necessary. There is a role also for implantation of artificial urinary sphincters but when done as an isolated procedure, close monitoring to detect possible detrusor changes is needed. Bladder neck closure is an effective measure when other methods have failed.

**Keywords: urinary incontience, neurogenic bladder, bladder neck closure, bladder neck reconstruction, urethral slings, artificial sphincters, injection of bulking agents, children**

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## INTRODUCTION

Urinary incontinence in children with neurogenic bladder and sphincter dysfunction (NBSD) is common (1). NBSD can be congenital or acquired. The most frequent etiologies in children are spina bifida, sacral agenesis, other spinal malformations (such as those associated with anorectal malformations), spinal trauma, and iatrogenic surgical injuries.

The pathophysiology of urinary incontinence in children with neurogenic bladder dysfunction (NVD) is often complex and should be clearly defined before deciding on which therapeutic alternatives are most likely to succeed.

Urinary incontinence results from an imbalance between bladder storage pressures and bladder outlet resistance. The anamnesis, voiding diary and urodynamic studies help in arriving at the correct therapeutic decision.

The scheme proposed by J. M. Guzmán helps placing patients in one of four groups based on the information obtained by urodynamic studies and simplifies decision making (**Figure 1**) (3). Patients in groups A and B have low outlet resistance and require procedures to increase it, which are the object of this review.

In most children with NBSD successful therapy can almost always be equated to dryness rather that true continence although such distinctions are often not clear in the literature (4). If we accept that the definition of incontinence is the involuntary loss of urine, then continence should be

the ability to voluntarily or involuntary avoid losing urine in the course of normal daily activities or during sleep. Of course, most patients with NBSD can seldom voluntarily control voiding and therefore it seems more appropriate to define a successful treatment in these cases as dryness, followed by the time period during which a patient is expected to be dry.

The backbone of treatment of NVD and NBSD is intermittent clean catheterization (5) since in most cases the bladder does not empty efficiently, particularly after procedures to increase outlet resistance and attain dryness have been performed. This includes patients who can occasionally void spontaneously with an implanted artificial sphincter.

Non-surgical treatments for incontinence in NBSD have been advocated by some (6) but are generally ineffective (7).

One problem in deciding which procedure is best for a given patient is the interpretation of the published literature which provides low levels of evidence and lacks uniformity in reporting results (8, 9). Therefore, it is difficult to reach solid conclusions from a review of this subject and personal experience and expert opinions are inevitably used in making clinical decisions.

The purpose of this review is to orient the interested clinician in this complex and often confusing topic. In this article we shall strive at objectivity and fairness but it must be recognized that lack of solid evidence in the literature (8) plus our long combined experience treating these patients may influenced our judgment. One of the authors participated in a review of the subject 18 years ago (10) and we will try to contrast the conclusions reached then with the conclusions reached in the present review.

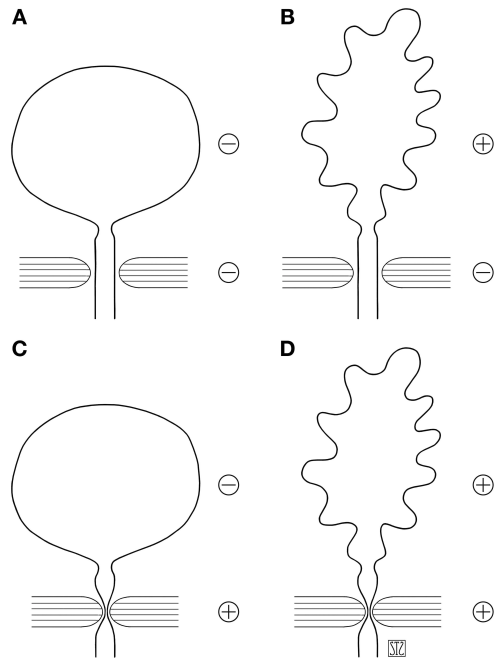


**FIGURE 1 |** Schematic grouping of causes of neurogenic incontinence based on urodynamic findings [adapted from González and Guzmán (2)]. **(A)** Detrusor and sphincter mechanisms hypoactive. **(B)** Detrussor hyperactive or hypocompliant, sphincter hypoactive. **(C)** Detrusor hypoactive, sphincter hyperactive. **(D)** Detrusor and sphincter hyperactive (dyssynergic). Reproduced with permission from Dr. Quek.

## MATERIALS AND METHODS

Review of the literature obtained by searching PubMed, Cochrane reviews and Google scholar under the words neurogenic urinary incontinence in children, artificial sphincter, sling, bladder neck reconstruction, and bulking agents among others. Abstracts and full text articles when available, in English, German, Spanish, French and Portuguese were reviewed. Abstracts that defined the criteria for patient selection, treatment employed, evaluation of outcomes and length of follow up form the basis for this review. Full text articles of the significant abstract were reviewed. Citations in the reviewed articles that were considered significant were included as well.

## RESULTS

The results presented derive from the review of the papers obtained in the literature search.

Surgical procedures to increase bladder outlet resistance can be grouped in 4 categories: (1) Periurethral injection of bulking substances to exert external compression of the urethral lumen, (2) Procedures to reconfigure the bladder neck, (3) Bladder neck suspension and periurethral slings and, (4) Artificial sphincters and other prosthetic devices, and (5) Bladder neck closure.

### Periurethral Injection of Bulking Substances

Numerous substances have been injected trans- or periurethrally in hopes to increase passive outlet resistance and to increase the leak point pressure.

Probably the first substance used was polytetrafluoroethylene paste reported more than 40 years ago (11) including in children (12), however its use was discontinued following reports of potentially dangerous migration of the substance to remote organs including the brain (13). Other substances followed, among others bovine collagen, autologous fat, polydimethylsiloxane, autologous chondrocytes, stem cells and dextranomer/hyaluronic acid (Dx/HA). In this section we review the relevant literature available for the use of bulking agents in children.

In the last 20 years some retrospective or prospective non randomized studies were published.

Injection of Dx/HA was mostly performed retrograde transurethral. Antegrade injection through an appendicovesicostomy (Mitrofanoff channel) or a suprapubic access was preferred in selected cases to obtain better view (14, 15). A suprapubic catheter or a catheter through the catheterizable channel was left indwelling for 3 days to 2 weeks (14).

Some authors reported repeated injections to achieve dryness (15, 16) while others found no improvement after second injections and did not recommend it (14, 17).

Most of the series have short term follow up. At 6 months of follow up two thirds of the patients had improvements in dry intervals (18, 19) with a decrease of the success rate to 50% at a follow up of 12 months (18). At longer follow up injection of Dx/HA resulted in improvement in half of the patients with dryness in 40% in the series reporting the best results (16, 17, 20). Recurrence of incontinence was considered mainly a sign for bladder deterioration and should call for an urodynamic evaluation (20).

Dean et al. published better results in using an antegrade injection technique and leaving a suprapubic tube for 1 to 2 weeks. They treated 34 patients, 28 with the diagnosis of neurogenic bladder and 6 non-neurogenic sphincter incompetence. In 19 patients a mean follow up of 11.7 months was available. Fifteen of the 19 patients (79%) reported significant improvement of the incontinence after multiple injections (15).

Dx/HA injections were performed primary or secondary after failed sling procedures or bladder neck reconstruction After failed sling procedures dryness was gained in 7–25% of the patients (14, 17, 20). After bladder neck reconstruction in patients with neurogenic bladder Faure et al. reported a continence rate of 54% (21).

The studies showed that endoscopic injection in the bladder neck is safe with a low complication rate (16).

Unfortunately the outcome of the injection was not predictable by urodynamic parameters, the endoscopic technique or by the volume of injected volume (14, 20). Females had a significantly higher success rate of 69 vs. 38% (20).

Alova et al. found no difference in success of further surgical procedures (bladder neck reconfiguration, artificial sphincter or sling procedures) after failed endoscopic injections (22).

Endoscopic injection of the bladder neck can be combined with transurethral injection of botulinum toxin A in the detrusor to enlarge the bladder capacity. However, in one series 16 children required 54 injections of botulin toxin and 13 children 24 injections of Dx/Ha over a 4 year period to attain "social continence" (19).

The use of stem cells injected in the area of the bladder neck and urethra is under investigation but no reports of their use in children with neurogenic sphincter incompetence are available (23).

## Procedures to Reconfigure the Bladder Neck

Attempts to induce urinary continence by reconfiguring the bladder neck (BNR) dates back almost 100 years when Young described an operation to correct incontinence in a patient with epispadias (24). The first published application of the Dees' modification (25) of the Young bladder neck reconstruction to patients with neurogenic bladder dates back to 1973 (26). Twelve years later González and Sidi published their experience in 14 patients with neurogenic incontinence treated with a combination of bladder neck reconfiguration, enterocystoplasty (EC) and intermittent catheterization (IC) after a rigorous determination of sphincteric incompetence using a combination of fluoroscopy and electromyography with excellent success in 7 patients. Patients thought to have adequate urethral resistance received only EC. Thirteen of 14 patients became dry (27). Four years later, the same group reported equal degrees of continence with BNR and implantation of an artificial urinary sphincter (AUS) but the complication rate was higher with the AUS (28). This series included patients who had received earlier models of the AUS, known to produce inferior results compared to more modern models. A Canadian group compared BNR in boys with colposuspension in girls. Girls became dry in a greater proportion of cases, however more girls than boys had an EC (29). More recently, Donnahoo et al. reported and initial success of 68% in 38 children with neurogenic incontinence. Ninety-two percent of the patients eventually required EC (30).

In a more recent study, Faure et al. reported on 55 children treated with BNR at a mean age of 7.6 years. Only 10 patients (18%) were considered continent after the isolated BNR and others received additional 2.29 bladder neck injections of a bulking substance. They found no differences in outcome between boys and girls but the results were better in neurogenic patients (54%) than in those with bladder exstrophy (30%) (21).

Other procedures have been described as alternatives to the Young- Dees repair with or without ureteral reimplantation (Ledbetter) (31). Tanagho described the elongation of the urethra with an anterior bladder tube (32, 33) to achieve urinary continence in a variety of conditions but the use of this technique in pediatric neurogenic incontinence has not been reported. Kropp and Angwafo reported a variation of Tanagho's technique creating a tube of the anterior bladder wall implanted submucosally in the midline of the trigone to create a valve mechanism. This technique was designed for children with neurogenic incontinence dependent on IC (34). Salle introduced a modification of this procedure intended to simplify it (35) and published a modification of the original procedure 3 years later (36).

In Kropp and Angwafo initial report 13 children with myelomeningocele reported that all patients stopped wearing diapers and were socially dry with a follow-up between 8 and 36 months (34). Using the same operation Waters et al. (37) reported on 49 patients with NBSD 72% of whom never had difficulty catheterizing per urethra. The problems with CIC occurred both early and late with equal frequency in males and females. The CIC problems were solved by changing the type of catheter and/or avoiding over distension. Two patients with persistent problems required a continent catheterizable channel.

Nakamura et al. (38) reported results of the Salle procedure in 12 children (9 with NSBD) Seven were completely dry (58%) at a mean follow-up time of 75 months. Three had experienced difficulties with urethral catheterization. After repeated procedures all patients became dry but most patients also had EC and a continent catheterizable stoma, indicative of the difficulties with urethral CIC.

Jawaheer and Rangecroft (39) reported results with the Salle procedure in 18 children with a mean follow-up of 24 months. Daytime dryness of 3 h or more was achieved in 61% but 5 remained incontinent. Four children experienced difficulty with urethral catheterization and 39 % required further operations.

Szymanski et al. (40) reported on a group of children who had either the Kropp and Angwafo ($n = 30$) or the Salle ($n = 8$) procedures with mean follow up of 7 and 10 years, respectively. The majority of children also had an EC and an abdominal catheterizable channel. There were no statistically significant differences in the 4 h dry interval between the 2 procedures (Kropp 81.3% and Salle 75.0%) but reoperations were frequent and ultimately most patients did not catheterize urethrally.

## Fascial Slings

Fascial slings operate by compressing the urethra and by elevating the urethra to an intraabdominal position to create resistance and thus increase the passive bladder outlet resistance and leak point pressure. The procedure was initially used to correct female non-neurogenic stress urinary incontinence and patients were expected to continue to void spontaneously. However, the use of slings in NSBD aims at creating an obstruction and spontaneous voiding cannot be expected, therefore clean intermittent catheterization is usually needed.

The first sling procedures were described at the beginning of the last century. McGuire et al. reported the first sling operations in children with NSBD in the 1980s using a rectus fascial sling (41).

Direct comparison of the reported results is limited due to combination of the sling procedure with other procedures (augmentation, BNR), various operation methods and sling materials, patient selection and definition of "continence". An early series by Barthold et al. reported significantly better results in females than in males with NBSD (42).

In one report, patients reported a better quality of life due to improved continence and longer interval between catheterization when they underwent sling operations with or without bladder augmentation (43).

Various materials have been used to construct the slings including autologous grafts, xenografts, and synthetic materials. In the last years in adult patients synthetic materials have been more widely used. In adolescents Garcia Fernández et al. reported achievement of a dryness interval for at least 3 h in 21/25 patients (84%) with the implantation of a mini-sling (polypropylene mesh with two lateral fixation arms) and only one major complication (44). Nevertheless, in children most reports relate to rectus fascial slings.

In isolated reports, sling implantations have been performed on outpatient basis (45) and with minimally invasive techniques (46). Castellan obtained continence in 51 patients of total 58 patients (88%) with rectus fascial sling procedure and bladder augmentation at follow up at mean 4.1 years. The authors consider the sling procedure as the procedure of choice but they emphasize the necessity of simultaneous bladder augmentation (47).

Snodgrass and Barber (43) reported complete dryness after bladder neck sling in 16 of 35 children (46%) whereas additional of a modified Young-Leadbetter bladder neck procedure (47) improved the results to 14 of 17 (82%) (43). The same group later reported no progressive deterioration in bladder compliance after bladder neck sling operation without augmentation at a mean follow up of 39 months (48). However, recently Noordhoff et al. (49) published the 10 year outcome of 60 patients who underwent bladder neck procedures (43 slings). In the majority of the patients a bladder augmentation (80%) and continent catheterizable urinary channel (97%) were eventually needed. Within 1 year only 15 patients (35 %) were dry and almost half of the children needed additional interventions.

Fascial sling implantations have a low complication rate. Chrzan et al. reported 2 urethral perforations managed conservative treatment in 89 operated children. In their experience, detrusorectomy (50) did not improve the rate of dryness but enterocystoplasty did (51). These authors also suggested that perineal access could help to avoid urethral injury in boys with small operating space or deformity of the pelvis. Dik et al. reported on 24 transvaginal approach to sling implantation in girls with spina bifida, 19 girls were dry after the initial procedure which was sometimes combined with a bladder augmentation or continent stomas. No patient had difficulty with catheterization or infectious complications (52).

## Artificial Urinary Sphincter (AUS)

The results of AUS implantation in children and young adults with neurogenic incontinence from several centers have been published (53). The first implantable AUS was reported in 1973, at a time when CIC was not yet widely accepted. In order to ensure bladder emptying, an external sphincterotomy in males and a Y-V plasty of the bladder neck for females was recommended (54). Since CIC has shown to be compatible with the AUS (55), such emptying enhancing procedures have been abandoned. One may consider separately continence or dryness, the possibility of spontaneous voiding vs. the need for intermittent catheterization, and the need for bladder augmentation. Dryness can be achieved with the AUS in 54 to 100 percent of patients (56–64). Some of the series cited included older models of the sphincter that were not as reliable or durable as the one currently available. If one excludes devices that were removed early because of infection or erosion, the results are even better, around 85% after 5 to 10 years.

Spontaneous voiding in children with NBSD can be expected in 22 to 47 percent, predominantly in patients with spontaneous emptying before implantation (65). However, spontaneous voiding may become difficult after puberty. Replacing the cuff for one of a larger circumference has not restored voiding in these patients (66). For this reason some have recommended waiting till after puberty to implant an AUS (67). From the point of dryness, however, the results are independent of the age of implantation (68).

The most frequent complications of AUS implantation are infection, erosion of structures in contact with the devise (bladder neck, urethra and skin) and mechanical failures. Infections could be minimized with meticulous aseptic technique and erosions by avoiding implantation on areas previously operated and with the new design of the cuff (69, 70). The durability of the AUS has improved significantly since the initial reports (53).

As with all effective means of increasing bladder outlet resistance, a bladder with sufficient capacity and compliance is essential for success and safety. However, even an acceptable bladder may undergo unfavorable changes after the outlet resistance is increased (49, 71). When the bladder capacity and compliance are insufficient, bladder augmentation prior or at the time of AUS implantation has been performed (72, 73). Nevertheless, it is questionable which urodynamic parameters are important to determine the need for augmentation (74, 75). In an attempt to reduce the likelihood of intestinal augmentation related complications others have combined the implantation of AUS with a seromuscular colocystoplasty with more than 85 % dryness at 2 years (76, 77). Others have sought to avoid the potential complications of mechanical malfunction of the AUS by implanting only the cuff at the time of an enterocystoplasty but most patients eventually required implantation of the entire AUS system (78).

## Bladder Neck Closure

Closure of the bladder neck has been reported as a salvage measure when other methods to induce continence have failed. Of course this is only applicable for patients with a good capacity and an alternative to urethral catheterization. Fistulas can occur requiring revision of the closure (79, 80).

# DISCUSSION

The results of this literature review put in evidence a wide variability in results. Nevertheless, it seems clear that little has changed since the 2000 report by Kryger et al. (81) except for a larger number of publications related to bulking agents and slings. The most frequently reported agent is Dx/HA. In general, injection of bulking agents have yielded disappointing results in NSBD as an initial or primary method of treatment. The attractiveness of the simplicity of the method is outweighed by its cost and the very frequent need of repeated injections to obtain at best, modest success. Perhaps the best application of injection of bulking agents is to improve dryness after slings or bladder neck reconstruction.

Bladder neck narrowing procedures, originally reported to correct the anatomy in patients with epispadias has been applied to patients with NSBD. The original Young procedure has suffered several modifications maintaining the principle of elongating the urethra proximally and narrowing the bladder neck. Procedures which create a one way valve, preventing leakage of urine from the bladder but allowing catheterization are more recent. In general the results of all techniques have been equivalent. They share the advantage of avoiding the use of prosthetic materials and being universally available. They all share the disadvantage of reducing bladder capacity, a factor that, added to the well-documented response of the detrusor to obstruction, makes simultaneous bladder augmentation mandatory. Problems with urethral catheterization develop frequently in long term follow up and so it seems wise to combine them with construction of a continent catheterizable channel. We have largely abandoned these operations in neurogenic patients in favor of slings, artificial sphincters or bladder neck closure.

Equally confusing is the literature regarding slings. Since in most reports with high success rates the sling placement has been combined with bladder augmentation and alternative routes for CIC (82), the effectiveness of the sling *per se* is difficult to discern. Only one report showed similar results of slings with and without enterocystoplasty (83). A large part of the problem lies with the difficulties in the preoperative evaluation of the outlet resistance in patients with small and non-compliant bladders (27).

The difference in outcomes between males and females varies also according to the reports (51, 84). In our practice, based on the literature and our own experience, we use slings in females dependent on CIC and largely in combination with a bladder augmentation. We routinely inform patients and families that problems with CIC might arise and that a continent catheterizable channel may be needed in the future.

We continue to implant AUS in males as our preferred method to increase outlet resistance and in females believed to be capable of spontaneous emptying (85). **Table 1** summarizes the effectiveness and potential problems of the various treatment modalities.

In our experience we reserve bladder neck closure when other methods have failed and the patient and her/his caregivers understand all the potential risks and potential solutions when catheterization of a full bladder is impossible.

The age at which continence should be achieved in these patients is also a controversial issue. While some emphasize the need to create the expectation of dryness at an early age (85) others propose waiting until after puberty (67).

The surgeon performing procedures to increase bladder outlet resistance assumes a long term commitment to educate and follow these patients given the risks of renal damage and indeed

**TABLE 1 |** Comparison of procedures to increase outlet resistance.

| Procedure | Effectiveness | Need for augmentation | Difficult urethral CIC | Need of second procedures |
|---|---|---|---|---|
| Injection of bulking agents | 7–54% | Unknown | No | Common |
| Bladder neck reconfiguration | 54–68% | 100% | Often | Rare if done with augmentation |
| Slings | 36–80% | 80% | Often | Common when used alone |
| AUS | 54–100% | 30% | No | 30% |
| BN closure | 90% | yes | N/A | 39% |

to life if the bladder becomes hostile or patient/caregivers compliance with CIC is not perfect.

## CONCLUSIONS

This review of the literature on the methods to increase bladder outlet resistance in patients with NBSD suggest that little progress in obtaining high level of evidence in the last 20 years. Surgeon's experience, personal preferences and open and honest discussion with patients and caregivers are essential to provide the best possible care for these challenging problems.

## AUTHOR CONTRIBUTIONS

RG and BL conceived the structure of the article. J-CB wrote the section on Slings and bulking agents. RG wrote the majority of the text. AL contributed to the preparation and editing of the manuscript. All authors contributed equally to the final version of the article.

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REVIEW
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# Applications of Laparoscopic Transperitoneal Surgery of the Pediatric Urinary Tract

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Application of laparoscopy in pediatric urology has evolved over more than 30 years coming from a merely diagnostic use for non-palpable testes to "interventional" laparoscopy to extirpative surgery and finally to the era of reconstructive pediatric laparoscopic urology, when in 1995 Peters described the first laparoscopic pyeloplasty in a child. Laparoscopic surgery in pediatric urology became implemented increasingly in the twenty-first century with now present-day applications including the complete variety of all kind of indications for surgery for pediatric urological pathology. This article aims to provide a comprehensive overview of current indications, techniques, and outcomes of laparoscopic transperitoneal surgery of the upper as well as of the lower urinary tract for urological pathology in the pediatric patient population.

**Keywords: laparoscopy, pediatric, urology, minimal, invasive, surgery, nephrectomy, pyeloplasty**

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## INTRODUCTION

Application of laparoscopy in pediatric urology has evolved over more than 30 years. Beginning with merely a diagnostic use of laparoscopy for cryptorchidism in the 1980ies, indications then were broadened from "interventional" laparoscopy such as the ligation of spermatic vessels for either Fowler-Stevens procedure or varicocelectomy to extirpative surgery with the first laparoscopic nephrectomy in 1991 and the first laparoscopic partial nephrectomy in 1993, respectively. In 1995, Peters performed the first laparoscopic pyeloplasty in a child, starting the era of reconstructive pediatric laparoscopic urology, which he described still in 2004 as the ultimate challenge in this field. Progressing rather slowly in the last century, laparoscopic surgery in pediatric urology became increasingly implemented in the twenty-first century also due to achievements in available technology such as smaller instruments, cutting edge dissection and suturing devices and not to forget the use of robotic surgery. Present-day applications include the complete variety of all kind of indications for surgery for pediatric urological pathology of the upper as well as of the lower urinary tract. Some of these laparoscopic procedures are meanwhile considered as the gold standard of surgical care in the field of pediatric urology as they could proof to be comparable to if not better than conventional open surgery in terms of functional outcome along with less morbidity due to minimal invasive access. This review should give a comprehensive overview to current indications, techniques, and outcomes of laparoscopic surgery focusing on laparoscopic transperitoneal surgery on the upper and lower urinary tract, respectively, in pediatric patients.

The laparoscopic transperitoneal approach has become a multi-used, standardized approach for a large spectrum of indications in pediatric surgery and pediatric urology, respectively. It offers a maximum capacity of working space (more than retroperitoneoscopy) and therefore is suitable for all age and weight groups in the pediatric patient population, ranging from the newborn to the

adolescent. It provides excellent overview, detailed visualization and augmentation which make laparoscopy the superior approach—particularly for complex anatomy and pathology, respectively (more than open surgery). Laparoscopy at present day and its current use in terms of "mini-laparoscopy," using smaller instruments and respective ports is truly minimally invasive. This does not only result in a superior cosmesis and thus the achievement of a nearly no-scar surgery, but also proved to provide advantages with regard to less postoperative pain, shortened hospital stay and faster recovery to normal activities. The question of why to perform a procedure laparoscopically rather than open should be replaced by "why not laparoscopically."

## LAPAROSCOPIC SURGERY ON THE UPPER URINARY TRACT

### Laparoscopic Nephrectomy

Laparoscopic nephrectomy has been described as a surgical first by Koyle et al. (1) Since that time indications have been decreasing for benign disease such as multicystic dysplastic kidney disease (MDKD) in terms of more restriction for removal, while indications for malignant tumors, particularly nephroblastoma (Wilms' tumor) are not only increasing but becoming legitimized through the corresponding treatment protocols.

Laparoscopic transperitoneal nephrectomy is approached through a standard 3-trocar access to the abdomen, with one 5 mm trocar at the umbilicus as for a 5 mm-scope, as well as 2 3 (2) mm-working ports in the upper and lower abdomen of the affected side, respectively. With regard to pediatric applications in a wide spectrum of available instruments and ports ranging from 2 to 12 mm the 3 mm-instrumentation proved to be the best compromise when it comes to minimal diameter along with maximal rigidity. As in general triangulation should be the goal with respect to kidney to be removed. Surgical steps include exposure of the affected kidney, either through a retro-colonic or a trans-mesocolic access to Gerota's fascia. Further dissection should focus on exposure of the renal pedicle as safe vascular isolation will be the primary goal. A dissection of the kidney out of the surrounding tissue prior to vascular isolation is not recommended due to loss of any stability of the kidney itself and consecutive difficulties to proper exposure of the vessels. Transabdominal hitching sutures may help to lift up and thus stabilize and expose the kidney, respectively. For vessel dissection and ligation different techniques are available as well as appropriate depending on size and diameter of the vessels such as monopolar cautery, harmonic devices, or most preferably vessel sealing instruments nowadays also available as 3 mm instrumentation. This may avoid the use of larger trocars for 5 mm-instruments such as clip appliers which are not available in smaller diameters so far. Ligation of both renal artery and vein must be safe, therefore suture ligation, clips, or again vessel sealing are appropriate. In any case the surgeon should be aware of additional either arterial or venous braches supplying the kidney which have to be taken down accordingly. Care should also be taken when dissecting the renal pedicle in order not to compromise the adrenal vein on the right side and for preservation of the adrenal gland in general in case the nephrectomy is not indicated for malignancy. After careful and complete vascular isolation the kidney then is freed from its surrounding tissue to complete. Further dissection of the ureter down to the bladder may then be performed depending on the indication and whether a radical nephro-ureterectomy should be achieved. The ureter may then be ligated using ligation, suture ligation, clips or simply a PDS-loop. However, in case of non-refluxing ureter it may just dissected without ligation of the distal stump. Some surgeons even advocate leaving the ureteral stump open if it is not reflexive. Finally, the kidney can be removed through the umbilical access which might need to be bluntly dilated, in case of a tumor-nephrectomy the use of a collecting bag is mandatory. In a regular case drainage of the retroperitoneal site is not necessary and should not be considered in case of a malignancy anyway. Repositioning of the colon will help to adequately cover the retroperitoneum and therefore further reconstruction of the retroperitoneum and closure of the peritoneum, respectively, is not necessary. In case that surgery at the bladder level is carried out additionally along with nephrectomy the specimen can be removed through the consecutive Pfannenstiel incision. Another special condition is nephrectomy for non-functioning kidney along with the indication for clean intermittent catheterization for neurogenic bladder disease. In this case nephrectomy should preserve the ureter which then can be used as a retroperitoneal continent catheterizable channel when brought out laparoscopically in the lower abdomen. This procedure can spare the patient additional incisions and in addition is somewhat "elegant" as the continent catheterizable channel leads into the bladder physiologically. The implementation of single-site, single-trocar techniques, summarized as Laparoendoscopic Single Site (or LESS) Surgery has been shown to deliver comparable results for nephro-ureterectomy for pediatric patients. The procedure can be achieved safely and efficiently, irrespective of age and weight. However, owing to the fact that single-site ports are not available for smaller children and infants different surgical approaches have to be considered. The question whether LESS provides even less trauma than in conventional laparoscopy remains doubtful.

Laparoscopic nephrectomy has become the gold standard for kidney removal in infants and children for benign indications and increasingly also for malignancies. It has been proven to be safe, effective and associated with a low complication rate while offering reduced morbidity due to surgical trauma, superior cosmesis and fast recovery. It therefore has been replacing the indication for open nephrectomy in the pediatric patient population (3). However implications apply for tumor-nephrectomy and therefore indicating laparoscopic nephrectomy have to take those in account according to current treatment protocols. In addition for tumor nephrectomy lymph node sampling is crucial for surgical staging and guiding further treatment. Thus, nephrectomy alone is insufficient in terms of an oncological correct tumor nephrectomy. The quality of adequate lymph node sampling laparoscopically yet has to be proven.

## Laparoscopic Partial Nephrectomy

Laparoscopic partial nephrectomy for benign indication is done for resection of a poorly or non-functioning moiety of a duplex system. The incidence of ureteral duplication ∼is 0.8%, however it represents the most common congenital anomaly of the urinary tract. The majority of duplex systems will not require surgical treatment if any. However, duplex systems becoming apparent with clinical symptoms such as obstruction and consecutive hydronephrosis—most likely in the upper pole and often associated with dysplasia, megaureter, and (ectopic) ureterocele, vesico-ureteral reflux (VUR)—most likely in the lower pole or incontinence due to ectopy of the (upper pole) ureter will require intervention. Currently accepted most common indications for partial nephrectomy of a non-functioning moiety are recurrent urinary tract infections (UTI), incontinence due to ureteral ectopy or VUR with consecutive hydronephrosis of a lower pole moiety. Laparoscopic and retroperitoneoscopic partial nephrectomy are widely accepted to be the gold standard while having replaced open surgical techniques.

Prior to laparoscopy a cystoscopy and subsequent stenting of the ureter which is supposed to be removed along with partial nephrectomy is recommended in order to facilitate later identification of both the ureters intraoperatively. Laparoscopic partial nephrectomy of a non-functioning moiety is carried out through a transperitoneal approach as described above for total nephrectomy. The patient is placed in a semi-supine position. Pneumoperitoneum (6–12 mmHg, depending on weight and age of the patient) is induced after positioning a 5 mm camera port in the umbilicus and again two 3 mm working ports. A 5 mm, 30° optic will provide adequate view. The kidney again is exposed through either a retrocolic or trans-mesocolic approach. Clear identification of renal vessel supply of the upper and lower moiety is key before dissecting in order to safely preserve the remaining moiety. Vascular control is mandatory before considering parenchymal dissection. For upper pole heminephrectomy care must be taken when mobilizing the upper pole ureter as it is crossing under the lower pole renal pedicle which has to be meticulously handled in order to avoid any damage to the vessels. This allows also clear differentiation between the upper pole vessels which then have to be dissected following ligation. In case of a lower pole partial nephrectomy the upper pole renal pedicle not necessarily has to be exposed however the surgeon must ensure the correct vascular supply and preservation of the remaining moiety. Vascular control is achieved with selective suture ligation, which can be facilitated using a hitching suture for better exposure of the moiety which is supposed to be resected. Other techniques for vessel ligation and dissection include clips (compromised by the necessity for a 5 mm trocar), the use of a harmonic knife, or nowadays available even in 3 mm a vessel sealing device which provides the ability of preparation and vessel sealing in one hand along with safety in terms of occlusion of the vessel. After vascular dissection a clear demarcation of the moiety to be resected is most often recognizable thus facilitating to determine the correct plane of parenchymal dissection. This may then be carried out using electrocautery or harmonic knife most preferably. Further dissection of the ureter as well as ligation and dissection may be performed as described above for total nephrectomy.

In case a reconstruction of the lower urinary tract a single-stage procedure is an option. The bladder is approached through a Pfannenstiel incision. This will allow removing the specimen easily. Resection of a corresponding ureterocele can be performed including an eventual bladder neck reconstruction and ipsilateral reimplantation of a lower pole ureter. Functional results proved to provide an excellent outcome in terms of renal function and bladder function (4). Early surgical intervention will avoid recurrent UTI and therefore prevent from renal scaring and consecutive loss of renal function.

Since Jordan and Winslow (5) reported on laparoscopic partial nephrectomy in 1993 it has increasingly gained acceptance (2, 6–8) despite that the operation is considered to be challenging and therefore offers limitations in terms of widespread among pediatric surgeons and pediatric urologists, respectively (3). However, with the advocated use of evolving hemostatic and dissecting devices that allowed to easier obtain vascular control and thus a more straight forward resection laparoscopic partial nephrectomy has gained more popularity among surgeons (3).

So far there exist no evidence whether the laparoscopic or a retroperitoneoscopic approach are of advantage for the patient. However, literature reflects a rather higher rate of conversion and a higher complication rate for retroperitoneoscopic partial nephrectomy than for the laparoscopic procedure. Esposito et al. published his results of a multicentric study including 102 patients undergoing partial nephrectomy in a 5 years period either by a laparoscopic or a retroperitoneoscopic approach (9). In his series, the overall complication rate was significantly higher for the retroperitoneoscopic group than for the laparoscopic group, respectively. In addition, the operating time for laparoscopy was significantly shorter than compared to retroperitoneoscopy. They concluded that laparoscopic partial nephrectomy seems to be faster and safer procedure and technically easier to perform in children compared to retroperitoneoscopic partial nephrectomy mainly due to a larger working space. In addition the possibility for complete ureterectomy in case of a refluxing system was considered to be an advantage along with laparoscopy. Multiple studies have been showing that in follow-up, that there is no functional loss of the remaining moiety (3, 4, 10, 11). Single site laparoscopic approaches have been frequently used for ablative surgery such as nephrectomy and partial nephrectomy in pediatric patients. They offer comparable results, however implications due to non-available port systems adequate to pediatric application may apply (12, 13). A recent published study considered the conventional laparoscopic approach the most preferable for nephrectomy and partial nephrectomy, respectively (14).

## Laparoscopic Pyeloplasty

Uretero-pelvic junction obstruction (UPJO) is the most common cause of hydronephrosis in infants and children. The gold standard in surgical care for UPJO has been open dismembered pyeloplasty through a retroperitoneal approach as described by Anderson and Hynes. When in 1995, Peters reported on the first pediatric laparoscopic pyeloplasty a new era of

reconstructive laparoscopic surgery on the upper urinary tract begun (15). Meanwhile laparoscopic dismembered pyeloplasty in children has become an established technique. It offers superior visualization of the anatomy, accurate anastomotic suturing and thus precise reconstruction of the UPJ which promises good functional results. Therefore, laparoscopic transperitoneal dismembered pyeloplasty can be considered as the gold standard for surgical treatment of intrinsic UPJO. Indication for surgery is given in case of a reduced differential renal function (DRF) of the affected side below 40%, a decrease of DRF in repeated examination, such as renal scintigram or MRI, respectively, a relevant urodynamic obstruction in renal scintigram or MRI, respectively, recurrent urinary tract infection (UTI) and/or pyelonephritis, subjective patient complaints, such as flank pain, or a special anatomical condition such as horseshoe kidney along with obstruction, respectively.

The conventional approach for laparoscopic pyeloplasty is a 3-trocar access to the abdomen, with one 5 mm trocar at the umbilicus as for a 5 mm-scope, as well as 2 3 mm-working ports in the upper and lower abdomen of the affected side, respectively. As in general triangulation should be the goal with respect to the renal pelvis to operate on. Surgical steps of laparoscopic transperitoneal pyeloplasty are defined as gaining access to the affected kidney, either through a retro-colonic or a trans-mesocolic access to Gerota's fascia. Following the incision of the fascia as well as of the fatty capsule of the kidney, a blunt/sharp dissection will expose the (dilated) renal pelvis. Further dissection and transabdominal hitching sutures will help to further expose the pyelon in a kind that a defined and safe resection of the uretero-pelvic-junction (UPJ) can be performed. Following the resection of the UPJ, the ureter is incised and spatulated on his lateral aspect in order to provide a sufficient length of ureteral wall for achieving a wide side-to-side anastomosis. For dissection and preparation different techniques are available and appropriate such as monopolar cautery, harmonic devices, or vessel sealing instruments. The anastomosis can be performed with either a single interrupted technique or a running suture as well. The single-interrupted sutures will offer more safety in achieving a watertight anastomosis and may be more tissue-sparing as well. The running suture may allow a rather time-saving technique however requires constantly application of tension to the thread in order to avoid loosening which might be the cause for urinary leakage later. Meanwhile barbed sutures are available down to metric sizes of 4/0, which may facilitate performing a running suture in this setting. Otherwise braided sutures in sizes of 6/0 for infants and 5/0 for older patients are appropriate. An inverting technique of suturing is recommended to avoid any suturing material to be exposed to intraluminal as this might cause crystallization at the thread with consecutive bacterial colonization. There is some ongoing discussion whether to stent the anastomosis and what kind of stent to use. The use of a transabdominal, trans-anastomotic stent technique described by Obermayr et al. (16) allows an atraumatic technique with does not require a second general anesthesia to remove the stent compared to the use of any kind of double-J-stents. Other techniques include double-J-stents, percutaneous nephrostomy stents and others. In a regular case additional drainage will not be required. The question whether to put a stent in and if so how long those should stay remain to the preference of the surgeon as there is so far no evidence in favor for one of the mentioned methods.

Laparoscopic dismembered pyeloplasty has evolved to become the gold standard for the surgical treatment of intrinsic UPJO since a surgical first in 1995 by Peters (15). It has been proven to be safe, effective, and associated with a low complication rate with excellent functional results (17–23). Laparoscopic dismembered pyeloplasty on the same hand offers low morbidity due to reduced surgical trauma, superior cosmesis, fast recovery and quick return to daily and social activities. It has been therefore surpassed open pyeloplasty in many centers as the gold standard for surgical management of UPJO. In addition laparoscopy seems to be as safe and effective as primary pyeloplasty for redo-surgery in case of failed pyeloplasty (24, 25). For the diagnosis of hydronephrosis in association with a horseshoe kidney the laparoscopic transperitoneal approach has been demonstrated to offer superior visualization of the anatomy, thus providing excellent functional results (26, 27).

Compared to open surgery there have been implications coming along with minimal invasive approach techniques. The most remarkable one is probably the less reduction of the renal pelvis as compared to the original technique described by Anderson and Hynes. However, different authors considered a less reductive resection of the renal pelvis not to be determinative in terms of the functional result (28, 29). Whether to use running or single-interrupted sutures, respectively, remains to the preference of the surgeon. There might be some higher surgical efficiency with the running suture method (30). One striking advantage of transperitoneal laparoscopic pyeloplasty is that the approach *per se* is a standard procedure for many indications in both pediatric surgery and urology. In addition it is applicable also for children below 1 year of age. There is sufficient evidence in literature that also in infants laparoscopic dismembered pyeloplasty has been proven to be a safe procedure providing the same functional outcomes as the open approach (31–33). In comparing laparoscopic multiport pyeloplasty with single-site approaches such as the trans-umbilical approach it could be demonstrated that although the cosmetic result with the single-site approach is satisfactory, the multi-port access did affect the shape of the umbilicus, thus the cosmetic result was considered to be better (34). Multiple studies were aiming to describe differences in between open, laparoscopic and robotic pyeloplasties, respectively. All of those demonstrate that patients undergoing robotic-assisted laparoscopic pyeloplasty had a shorter hospital stay and less request of pain medication however, there could be no difference shown in the success rates for open, laparoscopic and robotic-assisted laparoscopic pyeloplasty, respectively (35–37). In conclusion and with regard to a higher cost associated with robotic pyeloplasty thus making it less available to the majority of patients laparoscopic pyeloplasty is considered to be equal effective as all other available techniques and therefore should be considered as the true technique of choice for surgical treatment of intrinsic UPJO in children and infants.

## Laparoscopic Uretero-Ureterostomy

Along with the evolvement of laparoscopic dismembered pyeloplasty as becoming a standard procedure different kind of procedures for reconstruction of upper urinary tract pathology derived from the technique of laparoscopic dismembered pyeloplasty. In 2008, Lowe et al. already reported their series on duplex anomalies and laparoscopic reconstruction for obstructed, dilated segments (11). The procedures performed included pyelo-ureterostomy for incomplete duplication and lower pole pelvi-ureteric junction obstruction and ipsilateral uretero-ureterostomy along with distal ureterectomy for obstruction in a dysplastic upper pole with uretereal ectopy. The experience made as well as the results achieved are corresponding to the own experience. Placement of trocars and surgical exposure are analogous to that for laparoscopic transperitoneal dismembered pyeloplasty and as described above. As for duplex system surgery again the cystoscopic placement of an ureteral stent prior to laparoscopy is highly recommended in order to facilitate identification of the ureters during the laparoscopic operation. Suturing techniques again can be performed analogous to those used for pyeloplasty. However, due to limited calibers of ureters suturing must be meticulous in order to achieve a patent and non-obstructing anastomosis. Those procedures must be considered as challenging in terms of the required technical level of expertise as well as in terms of the absolute request for being successful in order to preserve the differential renal function of the affected duplex system. Observational studies (10, 11) could show that laparoscopic reconstructional surgery on the upper urinary tract using techniques deriving from pyeloplasty can successfully be applied for a various spectrum of procedures, however there is a relative lack of evidence in literature due to non-existing prospective and randomized studies.

# LAPAROSCOPIC SURGERY ON THE LOWER URINARY TRACT

## Laparoscopic Extravesical Ureteral Reimplantation

The most widespread laparoscopic procedure on the lower urinary tract in children is laparoscopic anti-reflux ureteral reimplantation. A first clinical experience with this laparoscopic application has been described by Janetschek et al. (38). They operated on six female patients girls for vesicoureteral reflux and recurrent urinary infections aged 6–10 years. The procedure performed was a laparoscopic ureteral reimplantation according to the well-established technique of Lich-Gregoir. When encountering mild unilateral stenosis, decompensating urinary tract obstruction as well as uncomplicated urinary tract infection they interestingly concluded that laparoscopic Lich-Gregoir antireflux procedure is a complicated operation offering no advantage compared to the conventional open operation (38). Lakshmanan and Fung re-defined the laparoscopic technique and concluded that the laparoscopic technique is comparable to open reimplantation techniques when reporting on their series of 71 children operated on for high grade VUR (39). With the evolvement and widespread of this technique too and the corresponding experience gained results obviously improved remarkedly as well as the perception of this procedure. Meanwhile the so called laparoscopic extravesical ureteral reimplantation (LEVUR) has become an accepted alternative to endoscopic treatment of vesico-uretereal reflux (VUR) in pediatric patients. However, the term reimplantation is somehow misleading as the technique used and described as Lich-Gregoir technique is not a true reimplantation but the creation of a sub-muscular path of the ureter done by extravesical dissection of the bladder detrusor muscle in order to achieve an anti-reflux mechanism. Current data in literature describe a success rate of up to 95% and a recurrence rate of VUR as low as of 4% in a patient population with VUR grade II–IV in a retrospective study (40). Authors concluded that compared to conventional open and endoscopic techniques LEVUR offers an acceptable success rate and better sustainability. A recent systematic review assessed five studies with a total of 69 LEVUR procedures performed representing a 96% success rate (41). However authors discussed that early success in terms of the anticipated anti-reflux procedure may be misleading when mid- and long-term effects and sequelae, respectively, will occur not until the 1st year after surgery. Thus, with regard to long-term outcomes in terms of preservation of differential renal function, absence of urinary tract infections and proper urinary drainage more evidence due to larger studies are warranted. Meanwhile reports on the application of laparoscopic-assisted extracorporeal ureteral tapering repair and ureteral extravesical reimplantation for primary obstructive megaureters attempt to show a success rate similar to the open procedure. However, again, larger trials and long-term follow-up are mandatory to justify this technique (42).

## Laparoscopic Appendico-Vesicostomy and Continent Catheterizable Channels

For the indication of complete bladder emptying in children with bladder voiding dysfunction such as neuropathic bladder dysfunction clean intermittent catheterization (CIC) is a viable option, preferably performed through the origine urethra. In 1980, Mitrofanoff described his technique of a continent appendico-vesicostomy for patients when transurethral CIC cannot be carried out for any reason (43). The laparoscopic approach for appendico-vesicostomy has been published by different authors already in 2004 (44, 45), however did not experience a widespread such as laparoscopic pyeloplasty so far. The surgical technique offers different options for the implantation of the appendix into the bladder by either using the anterior or the posterior wall, respectively. A different option for the placement of the appendico-cutaneostomy also applies by either using the classical Mitrofanoff-technique with the umbilicus or a rather pragmatic way by positioning the appendico-cutaneostomy into the right lower abdominal quadrant. In case of using the umbilicus care must be taken to prepare a triangular skin flap at the umbilicus up front when introducing the first trocar at the umbilicus in order to later properly implant the appendix. Two more working

ports may then be used left and right of the umbilicus to provide triangulation for approaching the appendix and bladder, respectively. As in the open technique identification of the appendix and mesoappendix is followed by ligation of the appendiceal basis and the dissection of the appendix while carefully preserving the blood supply through the mesoappendix. Next the bladder wall is dissected either starting from the urachus to attempt the anterior bladder wall or by approaching the posterior bladder wall. Herefore, a transabdominal suture, hitching the bladder dome up to the ventral abdominal wall will facilitate exposure. After cystostomy the anastomosis of the appendico-vesicostomy using the distal end of the appendix is carried out by using a single interrupted suturing technique. A subsero-muscular tunnel analogous to the technique of Lich-Gregoir and described above may be used to create an anti-reflux mechanism. Filling the bladder with sterile saline will facilitate dissection and cystostomy, respectively. A third working port may be used for bringing out the appendix at the desired place either to the umbilicus or to the right lower abdominal quadrant. In the latter case a sub-peritoneal tunnel may be therefore created. Care must be taken again for preserving the blood supply, non-torsening of the appendix and the respective meso-appendix as well as for an atraumatic technique in bringing the appendix to the skin. Deflating of the $CO_2$ pneumoperitoneum is mandatory in order to provide a proper alignment of the appendiceal channel. Prior to anastomosing the proximal end of the appendix to the skin ease of catherization must be proved and reproducible without obstruction until a Foley catheter is then left in place before finishing the procedure. During the check of ease of catheterization, the presence of any urinary leakage must be ruled out additionally. As an alternative to the Lich-Gregoir like anastomosis of the appendico-vesicostomy and in order to decrease surgical time and the demanding character of the procedure Weller et al. described an adaptation of the Schanfield ureteral implantation technique fixing the appendix to the anterior bladder wall using a single "U-Stitch" (46). After creation of a submucosal tunnel sharp dissection for the detrusorrhaphy follows and finally the mucosa is incised at the distal end of the submucosal tunnel. With a catheter in place a single U-stitch is performed and fastened extracorporeally with a Roeder knot in order to have an instrument available to guide the appendix into the bladder opening while the knot is then being tied. The use of an extra port may be an alternative to perform this step. The detrusor is then closed over the appendix thereby creating the antireflux mechanism. Authors concluded that this technique reduced operative time and made the procedure technically easier.

Since Hsu and Shortliffe published the first complete laparoscopic appendico-vesicostomy in 2004 (45) different authors have been reporting on both laparoscopic as well as robotic assisted appendico-vesicostomies in pediatric patients. However, operating times so far are of remarkable length ranging from more than 360 to still 180 min for a procedure when done alone while open surgery would require a much shorter operating time. With the modification described by Weller et al. (46) a significant reduction of the operating time could be achieved in a small patient series. As in the open procedure pitfalls and complications are mainly due to anastomotic leakage and persisting hematuria intra- and peri-operatively while issues with catheterization occur peri- and post-operatively but can compromise if not ruin the operative result. For laparoscopic appendico-vesicostomy limitations are to anatomy, i.e., lenght of the appendix, working space and last but not least experience of the surgeon. In terms of feasability but moreover the functional result the procedure must be considered as being highly demanding. However, in the observational studies published so far, intracorporeal laparoscopic appendico vesicostomy proved to be safe and effective offering a superior cosmesis but the same kind of potential complications as known from the open procedure (47).

Beside the laparoscopic appendico-vesicostomy other types of continent catheterizable channels or conduits, respectively, may apply to a laparoscopic approach. In the own experience the use of ureter when performed along with the indication for unilateral nephrectomy provided an elegant option for a modified Mitrofanoff-stoma, avoiding the necessity of implantation of the catheterizable channel into the bladder. Following nephrectomy and preservation of the ipsilateral ureter, the ureter is guided through a sub-peritoneal tunnel of the corresponding side of the abdominal wall before being delivered through the abdominal wall and getting anastomosised to the skin in either the left or right lower abdominal quadrant, respectively. Again ease of catheterization must be ensured.

## Laparoscopic Augmentation Cystoplasty

Bladder augmentation for surgical management of neuropathic bladder dysfunction is a procedure often performed in the context of other reconstructive procedures such as appendico-vesicostomy or bladder neck reconstruction resulting in complex reconstructive surgery individually stratified for the patient and therefore being demanding while requesting long operating times. The procedure of bladder augmentation can be performed using the (mega-) ureter when nephrectomy is anticipated on the same occasion. Auto-augmentation is another option however offers limited increase of bladder capacity and questionable functional results on the long run. At present day augmentation of the bladder using ileum—so called ileocystoplasty—represents a currently widely accepted standard of care. Ileo-cystoplasty itself requests resection and proper continuity-restoring anastomosis of the small bowel as well as of a continent anastomosis of the ileal segment to the mostly small and hypertrophic bladder thus being demanding in terms of suturing. Taking all the above mentioned into account, it may be justified to call a pure laparoscopic attempt to this operation ambitious even more when done in combination with other procedures such as appendico-vesicostomy.

Beginning in 1993, a first report on laparoscopic auto-augmentation was published by Ehrlich and Gershman (48), and followed by a first report on a laparoscopic bladder gastrointestinal augmentation using stomach in 1995 by Docimo et al. (49). At that time 5 trocars were used and stapling and suturing devices, respectively, to facilitate suturing. The operation took more than 10 h. It took 10 more years for

Shadpour to be the first reporting on 5 patients in whom ileo-cystoplasty could be performed without the use of stapling devices applying complete intracorporeal suturing using a 3-port laparoscopic approach (50). Pure laparoscopic enterocystoplasty could also be demonstrated by Lorenzo et al. (51) using a 3-trocar technique and stapling devices. Authors considered it to be an advanced procedure that is technically demanding (51). With the evolvement and increasing implementation of laparoscopic robotic surgery it could be shown that laparoscopic augmentation ileo-cystoplasty along with appendico-vesicostomy (Mitrofanoff) can be done purely intracorporeally including harvesting of ileum, bowel anastomosis, and the continent anastomosis of the ileal segment to the bladder in a 5-port-technique with the use of a robot (52). At the same time hybrid procedures as being a laparoscopic assisted uretero-cystoplasty intended to reduce surgical trauma, to be less invasive as well as to offer improved cosmesis (53). A rather recent publication reported on a combined laparoscopic-assisted nephrectomy, augmentation uretero-cystoplasty and Mitrofanoff-appendico-vesicostomy, using a 3 trocar technique and a Pfannenstiel-incision to access the bladder (54).

Although all those reports provided a less invasive option for bladder augmentation, proof of evidence in terms of being equivalent or even superior to conventional open surgery is lacking so far. However, those attempts for a more minimal invasive approach to even complex reconstructive surgery in pediatric urology demonstrate the potential of laparoscopic applications in pediatric urology in general.

## CONCLUSION

Application of laparoscopy in pediatric urology has evolved from a diagnostic use to "interventional" laparoscopy to extirpative surgery to reconstructive pediatric laparoscopic urology. Along with the progress in the expertise of pediatric surgeons and pediatric urologists achievements made with available technology lead to a highly complex spectrum of present-day applications including a large variety of indications for surgery for pediatric urological pathology of the upper as well as of the lower urinary tract. Some of these laparoscopic procedures are meanwhile considered as the gold standard of surgical care in the field of pediatric urology as they could prove to be comparable to if not better than conventional open surgery in terms of functional outcome along with less morbidity due to minimal invasive access. Others lack this kind of evidence but may understood as an attempt for a continuous progress in making pediatric urological surgery less invasive. This would result in not only superior cosmesis but providing a true benefit for the pediatric patient in terms of less postoperative pain, shortened hospital stay and faster recovery to normal activities. The future is bright. Single site surgery as well as robotic surgery are both areas of growth and continuous development in pediatric urology that will innovate future surgical treatment options (55). The use of 3D vision, along with articulating instruments will diminish the distinction between current robotic-assisted and conventional laparoscopy (56) thus providing the best out of two worlds in a hybrid application which will evolve to become not only a true alternative to current concepts but maybe a future standard of care. There are many more applications of laparoscopy for pediatric urology such as transperitoneal laparoscopic lithotomy or laparoscopic ureteral replacement (57, 58). So again, the question should be raised why not operate on laparoscopically.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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# Recent Trends in the Management of Bladder Exstrophy: The Gordian Knot Has Not Yet Been Cut

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Although enormous effort has been made to further improve the operative techniques worldwide, the management of bladder exstrophy (BE) remains one of the most significant challenges in pediatric urology. Today it is universally agreed that successful and gentle initial bladder closure is decisive for favorable long-term outcome with regard to bladder capacity, renal function and continence. Due to a number of reasons, including a lack of comparable multicenter studies, a range of concepts is currently used to achieve successful primary closure. We review the literature of the last 15 years on the current concepts of bladder exstrophy repair with regard to the time of primary closure (initial vs. delayed closure), the concepts of primary closure (single-stage vs. staged approach; without osteotomy vs. osteotomy) and their outcomes. There is a worldwide lack of multicenter outcome studies with adequate patient numbers and precisely defined outcome parameters, based on the use of validated instruments. The modern staged repair (MRSE) in different variations, the complete primary reconstruction of exstrophy (CPRE), and the radical soft-tissue mobilization (RSTM) had been the most extensively studied and reported procedures. These major concepts are obligatory stable now for more than 20 years. Nevertheless, there are still a lot of open-ended questions e.g., on the potential for development of the bladder template, on continence, on long-term orthopedic outcome, on sexuality and fertility and on quality of life. Management of BE remains difficult and controversial. Further, clinical research should focus on multi-institutional collaborative trials to determine the optimal approach.

**Keywords: bladder exstrophy, epispadias, urologic surgical procedures, delayed closure, osteotomy**

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## INTRODUCTION

Today the diagnosis of bladder exstrophy (BE) is usually made by prenatal ultrasound screening or by inspection after birth. In classic BE the bladder is completely opened in the lower abdomen so the edge of the inner surface of the bladder is fused to the abdominal skin. The evaginated bladder template is of different individual size. The mucosa of the bladder appears reddish and polyps may be seen on it. The symphysis is widely separated. In male an epispadic urethral plate covers the whole dorsum of the penis from the bladder template to the glanular grove (1). In females, the clitoris is split and is located next to the open urethral plate. The vaginal opening appears narrow and is placed anteriorly on the perineum (1).

Often pediatricians are consulted to assess the neonates, to initiate further diagnostics and to refer them to pediatric surgeons or pediatric urologists. Due to the very low prevalence

and various treatment approaches of this disorder, most physicians are not familiar with a standardized procedure.

The aim of BE repair is successful bladder closure and penile reconstruction in order to provide a capacious low-pressure and competent functioning reservoir as well as a good cosmetic appearance of the genitalia with unimpaired function and unobstructed urethra. By a successful primary closure normal renal function should be preserved.

The management of BE remains one of the greatest challenges in pediatric urology. While it is universally agreed that successful and gentle initial bladder closure is of utmost importance for development of bladder capacity and continence there are still numerous different concepts for the initial management of this condition (2). The main issues discussed are the time of primary closure (immediate vs. delayed closure), the type of BE repair (complete or staged), and finally the need of symphysis approximation with or without pelvic osteotomy.

Beyond doubt irrespective of the kind of reconstruction technique worldwide attempts are made to reduce the morbidity of management concepts.

## TIMING

Regardless of the different surgical techniques, timing of primary closure still remains a matter of debate. The initial closure may be performed within the first 48–72 h of life (immediate) or at ∼6–12 weeks of age (delayed).

Early closure is recommended to prevent environmental injury of the bladder mucosa (3). However, the impact of early closure in respect of the incidence of inflammation, fibrosis, or even malignant changes remains unclear. Rösch et al. characterized the histology of polyps and mucosal biopsies excised during primary delayed surgery (4) and compared their findings with previous data concerning biopsies obtained during early closure in the neonate. In comparison to the specimens of newborns with BE (5) active inflammation was more common but fibrosis and more severe inflammation was not more frequent in delayed closure. Ferrara et al. suggested that some microscopic changes, such as squamous metaplasia, reverse to normal after bladder closure (6, 7). Literature on mucosal changes in early life in BE is rare. Including data of subsequent series (8, 9), there is no advice for histologically or immunohistochemically detectable premalignant changes after the interim of 6–8 weeks and in comparison to early bladder closure neither fibrosis nor more severe inflammation seems to be more frequent after that time.

Anesthesia and analgesia are challenging in primary BE repair especially in early closure. Some factors associated with perioperative cardiac arrest have been identified (10, 11). It was found that the largest number of perioperative complications occurred in newborns (10, 12). Further, on there is a higher oxygen uptake rate in newborns. This means a severely increased risk of hypoxia damage in cases of circulation or ventilation problem during surgery or post-operatively. One of the most important determinants of successful bladder closure is effective local analgesia. There is evidence that neonates exposed to extreme stress during delivery, or to a surgical procedure, react to later noxious procedures with heightened behavioral responsiveness (13). The use of continuous caudal epidural analgesia allows application of local analgesia minimizing the use of intravenous and oral opiate analgesia (14). It also helps to wean the babies from the respirator and decreases pediatric intensive care unit length of stay furthermore the minimal use of opiates may also decrease gastrointestinal motility disturbances (2). In general neonatal epidural analgesia is feasible but it is a given fact that the application of an epidural catheter in a 6-weeks old infant is more reliable.

Also with regard to the development of renal function there is a more stabilized situation after the 6th week of life (15):

- Acid-base-regulation in the neonate is characterized by a reduced threshold for bicarbonate reabsorption. There is also an inability to respond to an acid load, this improves by 4–6 weeks postnatally.
- Renal concentration capacity is reduced in the first 2 month of live.
- In the neonate glomerular filtration rate (GFR) is low and doubles in the first 2 weeks and doubles again in the following 2–3 weeks.

This immature situation of renal function in the newborn period means a high risk for long-term kidney function. Even marginal iatrogenic fluid imbalance or temporary post-renal obstruction (e.g., stent or catheter obstruction) may provoke irreversible renal impairment.

Last but not least bonding after birth is of eminent importance of developing infant's self-regulation and further interaction to mother and father (16, 17). In particular, separation may delay and disrupt bonding in parents. Another advantage of delaying surgery is initiating breastfeeding (18, 19). In addition, the time between birth and initial repair is useful to the parents to get psychological support if desired and to prepare themselves for the procedure and the lengthy recovery period following.

## PREOPERATIVE MANAGEMENT

In case of delayed management, only a few diagnostic measures are required preoperatively. Besides the ultrasound of the upper urinary tracts and the hips an echocardiography is recommended, recent studies indicate that there is an increased risk of associated congenital heart failures in BE patients (20). Further diagnostics like MRI or computer tomography are not necessary. Until surgery the bladder template is covered with topical ointment compresses against inflammation and alteration of the mucosa (1). There is no need for an extended hospital stay after delivery or even stay on the intensive care unit. Antibiotic prophylaxis is not necessary and not recommended in order to avoid development of resistance or topical fungal infection.

## MAIN SURGICAL CONCEPTS

Already at the beginning of the twentieth century there are first reasonable attempts to treat this defect surgically. Since the 50's

numerous different concepts are introduced to reconstruct BE under functional and aesthetic aspects.

Three of them has been the most extensively studied and reported procedures.

The modern staged repair (MSRE) (21), the complete primary reconstruction of bladder exstrophy (CPRE) (22) and the radical soft tissue mobilization (RSTM) (23).

The traditional staged reconstruction popularized by Gearhart and Jeffs has been a standard approach for many years (1, 21). The so-called **"modern staged repair" (MSRE)** is currently advocated as a modification by John Gearhart. He made this three-stage concept popular worldwide (1, 24). The bladder template the posterior urethra and the abdominal wall are closed within the first 2 days of life and the pelvic ring is adapted. Epispadias repair follows at the age of 6–9 months. In females, genital reconstruction is mostly included in the first operative procedure. As a third step, bladder neck reconstruction and simultaneously an antireflux plasty are performed when bladder capacity reaches a minimum of 85 cc. and the child is ready for continence training (1).

An antireflux plasty is always conducted with the bladder neck reconstruction (1).

Currently multiple variations of bladder neck reconstruction within this concept are established in different parts of the world. The restriction of all the above named modifications is that they can create essentially only a kind of obstruction of the bladder neck instead of a functional continence mechanism. Moreover, obstruction is not necessary for bladder growth, quiet the contrary, initial bladder neck surgery might have negative effects on the development of a functional bladder (8).

As a sort of striking a new path *Grady and Mitc*hell introduced the **complete primary repair of bladder exstrophy (CPRE)** in hope it would more closely mimic the normal anatomy and therefore physiology of the normal bladder (22, 25). This approach includes bladder closure and reconstruction of the penis using the penile disassembly technique. This procedure is implemented on the basic concept that the primary defect of bladder exstrophy results from on anterior herniation of the bladder. It hence appears to be necessary to treat the bladder, the bladder neck and the urethra as one entity in order to transfer them successfully and permanently into the pelvis. The penile disassembly technique is performed simultaneously with bladder neck reconstruction (26). Unfortunately in the long-term follow-up in numerous cases a bladder neck reconstruction was necessary to gain social continence (27). Further on concern is raised for the risk of future detrusor underactivity as well as erectile function due to the "unimpeded radical mobilization" of the bladder-urethral plate complex in the direction of the pelvis (25).

The **radical soft tissue mobilization (RSTM)** introduced by Kelly (23) may be considered as the so far most consequent concept off the classical bladder neck reconstruction. The unique aspect of this technique is the dissection especially of the pelvis and the corpora cavernosa from the ischiopubic rami including the periosteum with the attachments of the voluntary and unvoluntary sphincter muscles and the pudendal vessels and nerves (23). These muscles are used as a wrap around the new created posterior pelvic urethra to work as a continence mechanism. No osteotomy is performed since RSTM allows sphincter reconstruction and abdominal wall closure without tension.

RSTM is an anatomical reconstruction of BE generally performed as part of a two-staged strategy following successful neonatal closure. Complete delayed bladder closure with RSTM is a recently published modification of this concept (6).

However, the Kelly repair remains a long and technically challenging procedure even in experienced hands with a very possible risk of ischemic damage of the erectile tissue (28). Further on, leaving the symphysis without adaptation poses a certain risk with regard to the long-term abdominal wall stability and the gynecological outcome, during pregnancy as well as in terms of early prolapse of uterus (29).

**TABLE 1 |** Wide range of continence rate of the different approaches depending on definition of continence and observation period.

| Approach | Continence rate (%) | Literature |
|---|---|---|
| MSRE | 74 | Gearhart et al. (30) |
| | 62 | Gupta et al. (31) |
| | 22 | Dickson et al. (32) |
| CPRE | 80 | Grady et al. (22) |
| | 74 | Hammouda et al. (33) |
| | 23 | Arab et al. (27) |
| RSTM | 73 | Kelly et al. (23) |
| | 70 | Jarzebowski et al. (34) |
| | 33–67 (female)<br>44–81 (male) | Cuckow et al. (35) |

## CONTINENCE RESULTS

Although there are numerous publications on BE, most of the outcome are recorded retrospectively as single-center or single-surgeon-studies. Different definitions observation periods, end-points, and successful outcome, in particular the definition of "continence" and possibly further surgeries lead to quit different results (**Table 1**). Although first results of all approaches show a very promising high rate of continence, long-term studies that must mean at least 20 years of follow-up (36) reveal disillusioning results. This fact also seems in our experience to be more realistic. Moreover, Woodhouse et al. postulate that more than 80% of the reconstructed children can achieve continence, but there is some evidence that in 70% this is lost with time (36).

## EPISPADIAS REPAIR

The following procedures are the basis to ensure a functional and cosmetically acceptable outcome (1):

- The remove of dorsal chordee
- Reconstruction of the urethra
- Glandular reconstruction
- Penile skin closure

**TABLE 2 |** Outcome of symphyseal approximation with and without osteotomy.

| Literature | *N*= | Median age at investigation | Type of osteotomy | Symphysis with cm (range) |
|---|---|---|---|---|
| Kaar et al. (44) | 13 (11 m., 2f.) | 24 years (17–36 year) | Posterior osteotomy | 5.8 cm (4.1–11.2) |
| Satsuma et al. (45) | 9 (3m., 6f.) | 8 years (5 month−17.5 year) | Anterior or combined osteotomy ($n = 3$) Posterior osteotomy ($n = 6$) | 3.75 cm (1–7) |
| Castagnetti et al. (46) | 14 | 9.7 years (3.1–17.8 year) | No osteotomy ($n = 6$) Osteotomy | 4.9 cm (2.4–6.6) |
| | | | various types ($n = 8$) | 4.2 cm (2.5–10.1) |
| Kertai et al. (43) | 17 (14 m., 3f.) | 18.2 years (13–28 year) | Symphysis adaptation without osteotomy | 5.1 cm (2.8–8.5) |

*Silver* was able to show that the corpora cavernosa in BE are very much shorter than in age-matched controls (37). The reduced length of the penis is thus primarily an acquired deficit of corpora cavernosa tissue and not only a consequence of the chorda and the bilateral fixation to the ascending pubic rami, which was assumed for a long time.

*Ransley* introduced the concept of releasing dorsal chordee by incision and dorso-medial anastomosis of the corpora cavernosa above the urethra (38). Today, the *Cantwell-Ransley technique* is a modification and further development in which a very much more effective relocation of the urethra between or below the corpora is possible by complete mobilization of the urethral plate from the corpora (**Figure 1**).

The characteristic feature of the *Mitchell technique* is the complete dissection of the penis into 3 parts (26): The urethral plate, the right corpus cavernosum with hemiglans and the left corpus cavernosum with hemiglans (26). After tubularization of the urethral plate, it is positioned ventrally between the corpora cavernosa. If the urethra is too short, the neomeatus hast to be positioned on the ventral part of the penis. Hence, most patients require an additional procedure for hypospadias repair. Further on concern is raised for future erectile function due to shearing and stretch injury to the nerve fibers during complete penile disassembly (25).

Perineal dissection during the RSTM allows complete exposure of the corpora cavernosa (23). Incision of the periosteum of the ischio-pubic rami until the Alcock's canal allows a full mobilization of both corpora. Mostly urethral plate is short and would retract the corpora and shorten the penis. Therefore, in most cases distal urethra is disconnected from the glans and placed in hypospadic position. After readaptation the corpora were anchored to the neosymphysis using unabsorbable sutures.

Owing to extensive mobilization, all techniques of epispadias repair have in common that they require a very meticulous dissection in the anatomical layers using magnification glass in order to maintain the blood and nerve supply of the individual structures to avoid erectile dysfunction and corporal atrophy.

Nowadays, the reconstruction of **female genital** becomes less invasive. The split clitoris is usually left untouched to protect the delicate nerve supply and to avoid scaring caused by later re-dehiscence of the symphysis. Recently Benz et al. were able to show that contrary to the corpora cavernosa in boys, girls with BE have the majority of the clitoral body anterior to the pelvic attachment (39). Skin and tissue retraction in the mons pubis area is cosmetically improved by mobilizing adjacent inguinal tissue and rotating it medially into the affected area. In about 2/3 of these patients vaginoplasty is advisable (1). Episiotomy or an introitusplasty using a triangular skin-flap (*Fortunoff-flap)* can be performed to prevent repeated dilatations during childhood (1, 40). This should be done just in before or during puberty.

## NEED OF OSTEOTOMIES

The **role of osteotomy** is still a main topic in initial bladder closure. For a long time osteotomy was regarded essential for a successful outcome. But there are also reports confirming no difference in success of bladder closure (1, 41, 42). However, it is known that symphysis diastasis recurs after all commonly used pelvic closure techniques (43). There are only a few studies dealing with pubic diastasis after various types of pelvic osteotomy in a reasonable follow-up (36–39). According to these data the distance of recurrent mean pubic diastasis is not differing relevant in the long-term with and without osteotomy (**Table 2**). Castagnetti et al. compared patients after initial closure with and without osteotomy prospectively (46). In the long-term follow up they found no significant difference in the wide of pubic diastasis, in the number of exstrophy-related surgical procedures, in the incontinence rate and in the number of patients needing clean intermitting catheterization for bladder emptying (46). Kertai et al. was able to show that despite BE-specific hip morphology, long-term hip function was not impaired in adult adolescent patients after symphysial approximation without osteotomy in infancy. The symphysis diastasis after this procedure was also comparable to available post-osteotomy data in the long-term (43). In a case series published by Mushtaq et al. (2), primary bladder closure without osteotomy and post-operative immobilization was successful in 70 of 74 patients (95%) in respect to bladder closure. In our department pelvic ring closure could be achieved during the last 15 years without osteotomy in all infants with classical BE younger than 8 weeks (1, 41).

In female patients symphysis approximation may prevent uterine prolapse regardless of the type pelvic adaptation (with or without osteotomy) (1).

Nevertheless, based on the available literature and contemporary variability in worldwide practice, it would appear that there is currently no consensus regarding the

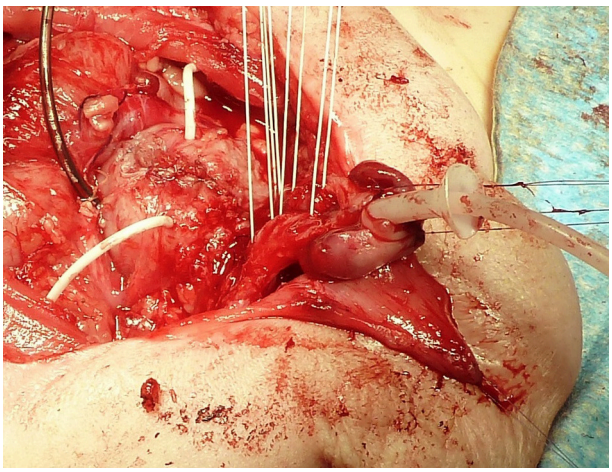

**FIGURE 1 |** Bladder after primary closure drained by a suprapubic and two ureteral catheters. Four sutures are prepared for approximation of the separated corpora carvernosa over the tubularized urethra with an indwelling stent. The corpora are rotated laterally to correct the dorsal deviation of the penis.

necessity of osteotomy in primary BE repair. Although not universal, most would agree on the efficacy of osteotomy in redo cases (47).

## CURRENT RESEARCH GAPS AND POTENTIAL FUTURE DEVELOPMENTS

A critical look into the historical data indicates that almost nothing is new in the philosophy and treatment of BE since more than one century ago. Nevertheless, due to the benefits of new technological developments there was an appreciable progress in BE reconstruction during the last decades of the last century. All these major concepts are obligatory stable now for more than 20 years and ensure a safe primary bladder closure including an appealing appearance of the genitalia in experienced hands. Apart from that, there are still a lot of open ended questions e g., on the potential for development of bladder capacity, on continence, on long-term orthopedic outcome, on sexuality and fertility and on quality of life.

First of all further clinical studies should focus on multi-center prospective trials with exactly defined outcome parameters to find an optimal management (29). In addition basic research is necessary to elucidate the morphological changes in the pattern of detrusor muscle and epithelium to establish a basis for understanding the preconditions for development of bladder-function and -capacity in BE.

Beside, further immuno-histologic studies of the bladder template, genetics will help to assess the prognosis in a realistic way. The systematic and comprehensive application of modern molecular genetic techniques in large BE cohorts has started to identify putative disease causing genes and regions in the genome for Mendelian and multifactorial BE phenotypes (48). Such studies can offer new diagnostics, and provide a more exact estimation of recurrence risk in affected families (48). Parallel functional analysis of the respective embryonic pathways offers a more profound understanding of the molecular mechanisms underlying the embryology of the urogenital tract (48). Moreover, understanding the respective embryonic pathways can help to explain related genitourinary malformations (49).

Tissue engineering aims to develop alternatives for current techniques in which intestinal tissue is used for patients with inadequate development of bladder capacity. Recent studies using tissue engineered extracellular matrices or acellular scaffolds with growth factor in animal models are promising (50, 51). However, there are scores of open issues which need to be fully clarified and defined before tissue-engineering in urology progresses from bench to bedside in BE-reconstruction.

Muscle-derived stem cells (MDSC) may offer further benefits in regenerative medicine (52). Several clinical studies have evaluated the effect of cell therapy with autologous myoblasts in the treatment of urinary incontinence, and have shown promising results (53, 54). Against this background MDSC therapy might represent a minimally-invasive procedure also in the treatment of patients with isolated epispadias in the near future. Latest studies are promising to generate differentiated urothelium from stem cells isolated from the urine. Urothelium obtained this way seems to be comparable with native urothelium and provides a valuable tool for reconstruction of the urinary tract as well as offers the chance for further studies in urothelial dysfunction (55).

Management of BE remains difficult and controversial. Further basic and clinical research should focus on multi-institutional collaborative trials to determine the optimal approach. Irrespective of that multidisciplinary ideation is in demand to generate new functional reconstruction concepts for this condition.

## AUTHOR CONTRIBUTIONS

All authors contributed conception and design of the review, wrote sections of the manuscript, contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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# Current Indications and Techniques for the Use of Bowel Segments in Pediatric Urinary Tract Reconstruction

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Today, there are few indications for the use of bowel in pediatric urology. This is in large extent due to the successful conservative therapy in patients with neurogenic bladder and the improved success of primary reconstruction in patients with the bladder exstrophy-epispadias complex. Only after the failure of the maximum of conservative therapy or after failure of primary reconstruction, bladder augmentation, or urinary diversion should be considered. Malignant tumors of the lower urinary tract (e.g., rhabdomyosarcomas of the bladder/prostate) are other rare indications for urinary diversion. Replacement or reconstruction of the ureter with a bowel segment is also a quite rarely performed procedure. In this review, the advantages and disadvantages of the different options for the use of bowel segments for bladder augmentation, bladder substitution, urinary diversion, or ureter replacement during childhood and adolescence are discussed.

**Keywords: urinary diversion, urinary diversion complication, urinary diversion-methods, children and adolescent, surgical complications**

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## INTRODUCTION

Today, the indication for the use of bowel segments in pediatric and adolescent urology for bladder augmentation, substitution, or continental urinary diversion has been markedly decreased.

Nowadays, the establishment of early conservative therapy with intermittent catheterization and pharmacotherapy in patients with a neurogenic bladder due to spina bifida seems to lead to a reduction in surgical therapy—at least early in life (1–3). After establishment of the conservative treatment, the numbers of augmentation did not decrease any more, at least in the USA (4, 5). In patients with bladder exstrophy or incontinent epispadias, primary reconstruction has become the most accepted approach (6, 7). If conservative therapy or primary reconstruction does not lead to the desired outcome or if the function of the upper urinary tract is endangered, bladder augmentation, or urinary diversion should be considered (8). The indication for radical cystectomy is extremely rare in children and adolescents (9). The replacement of the ureter in this age group is even more rare (10–18).

Considering the use of bowel segments, the special situation of the patients and their family's abilities and conditions, previous operative interventions and last but not least the expectations and wishes of the patient, their families and the surgeon must be considered. It is also essential, that the patient and parents have to be informed in detail about the advantages and disadvantages

of the various forms of urinary diversion, their surgical complications and metabolic consequences (2, 19). Furthermore, it is advantageous, that an uro-therapist or stoma-therapist supervises the patients right from the beginning and trains the postoperative care in detail. This is the best way to respond to unrealistic expectations or fears.

In the following, the different forms of urinary tract reconstruction performed during childhood and adolescence such as bladder augmentation, bladder substitution, urinary diversion, or ureter replacement are described and discussed concerning their advantages and disadvantages.

## BLADDER AUGMENTATION AND SUBSTITUTION

A low-compliance, small-capacity bladder is the classical indication for bladder augmentation. The patient and/ or caregivers should be able to empty the augmented bladder using clean intermittent (self) catheterization (CI(S)C). If catheterization via urethra is difficult or impossible due to anatomical or orthopedic problems (the patient cannot easily reach the urethra to perform the CISC), a continent catheterizable stoma ("Mitrofanoff" stoma) should be offered (20). In patients with an incompetent urinary sphincter, who need a bladder neck procedure, the placement of a continent catheterizable stoma should be also discussed. In patients who need a bladder neck closure, a stoma needs to be placed either at the umbilicus or in the right or left abdomen, depending on the anatomy (position of the belly button, length of the mesentery of the appendix, position of the bladder in relation to the umbilicus etc.).

For bladder augmentation, gastric, ileal, ileocecal, and colonic segments as well as the ureter can be used (2). During the operation, it is essential that the bladder is opened widely ("clam technique") to prevent the so-called "hourglass" phenomenon (21, 22). Unfortunately, in some cases the mesenteric arteries of the ileal segment are not long enough to reach the trigone due to the wide opening. In these cases, using a colonic segment is a better choice/ option.

As early as 1899, an ileal segment was used for bladder augmentation in patients with bladder exstrophy (23, 24). In the late 1970, ileum was increasingly used to increase bladder capacity (25). The ileal segment is detubularized and reconfigured in a U- or S-shape to form a large spherical reservoir based on the residual bladder (21, 22).

The ileocecal segment was first used in the middle of the last century for bladder augmentation (26). There is no advantage for using the ileocecal segment compared to an ileal segment. However, if the ileocecal segment is used for augmentation, the appendix can be embedded in the taenia libera and used as a continent catheterizable stoma similar to the ileocecal pouch (MAINZ pouch) (27). If ureter reimplantation is necessary e.g., due to obstruction or symptomatic reflux, the ureter(s) can be reimplanted in the terminal ileum and the ileocecal valve serves as reflux protection (28).

The sigmoid colon was already used for reconstruction at the beginning of the last century. Detubularization started in the middle of the last century (29, 30). The sigmoid colon is closely located to the bladder and in cases, in which the ileum cannot be used (e.g., due to a short mesentery, Chron's disease etc.), it can easily serve for augmentation to increase bladder capacity. Disadvantages of the use of sigmoid segments are the lower capacity, higher pressures, and lower continence rate—at least in most of the studies in patients with a neobladder (31–34). To avoid metabolic complications due to the use of intestinal segments, autoaugmentation with partial detrusorectomy or detrusormyotomy creating a diverticulum have been performed. However, the results are conflicting in the literature (35–38), and mostly those with a preoperative bladder capacity of 75–80% of the expected volume have a benefit from the operation (39, 40). Also, the seromuscular cystoplasty (41, 42)—performed also to avoid metabolic consequences/complications—has not proven to be as successful as the standard augmentation with intestine (43).

Particularly in patients with neurogenic bladder dysfunction, the choice of the intestinal segment gains importance. In patients with preoperative soft stool or occasional diarrhea, the stool frequency can increase and a new fecal incontinence may occur. The reconstruction of the ileocecal valve as part of the creation of an ileocecal pouch (MAINZ pouch) has not proved to be successful in the long term (44, 45).

Since 1978 stomach has been used for augmentation particularly in patients with short bowel syndrome and/or impaired renal function (46, 47). Common complications are hyponatremic hypochloremic alkalosis and "haematuria-dysuria" syndrome in more than 1/3 of the patients (48, 49). Furthermore, it could be demonstrated that quite aggressive secondary tumors can occur starting 10 years postoperatively (50–53). Today, gastric segments should not be used anymore—if possible—due to these serious complications.

In contrast to the use of any bowl segment using the ureter to enlarge the bladder has no metabolic consequences. This method was first mentioned in 1973 (54). Thus, theoretically it would be the best material for bladder augmentation. Unfortunately, the combination of a functionless kidney with a significant dilated ureter that is well-supplied with blood vessels is very rare. Furthermore, the re-augmentation rate in larger series could be up to 73% (55, 56).

Urinary continence cannot always be achieved by bladder augmentation alone, especially in patients with neurogenic bladder dysfunction. Thus, 14 out of 21 patients in the cohort of Kaufmann et al. (57) and 20 out of 59 patients in the study of Heschorn et al. (58) remained incontinent. Autologous slings or artificial sphincters can be used to improve continence. Implantation can may be performed simultaneous to the augmentation or delayed (42, 59).

As vesicoureteral reflux is mostly secondary, the treatment is primary related to bladder function (60). Patients with a high-grade reflux before augmentation have a higher risk for persistent symptomatic reflux after the enterocystoplasty

(61) and simultaneous ureteral re-implantation in high grade symptomatic reflux, especially in those with low-pressure high-grade reflux, should be discussed.

Today, bladder augmentation is usually performed by using an ileal or sigmoid segment, depending on the surgeon's preference and experience. If the ileal segment cannot be used due to anatomical or functional reasons, the sigmoid colon can be used and vice versa. Gastric segments should be avoided due to the high complication rate. If a continent catheterizable stoma is necessary, the appendix is the method of choice.

## CONTINENT ANAL RESERVOIRS

Continent anal reservoirs have been the first kind of continent urinary diversion. The history of continent anal diversion started in July 1851 in London. Sir John Simon performed a fistula between the ureters and the rectum in a boy with bladder exstrophy. Unfortunately, the boy died 1 year later with multiple ureteral stones and obstruction of the upper urinary tract. In October 1851, Mr. Lloyd—as well from London—performed a similar operation in a boy with exstrophy, who died 8 days later due to peritonitis (62, 63). These two first cases demonstrate the problems of urinary diversions performed in these days—infection and obstruction. Due to these problems, different kind of anal reservoirs have been created, such as the Maydl procedure, the Gersuney, the Heitz-Boyer and Hovelacque or Mauclaire bladder as well as their modifications (64–72). At the beginning of the last century, anal reservoirs had been the only option for a continent urinary diversion. In the 1930s and 40s, the ureterosigmoidostomy was used for continent urinary diversion, especially in patients with malignant disease (73). Due to the high number of surgical and non-surgical complications and consequences as well as the increased risk of secondary malignancies, this type of urinary diversion fell into disrepute (73, 74). At about the same time, Eugene Bricker popularized the ileal conduit as an incontinent form of urinary diversion—the so-called "Bricker Bladder" (75). To overcome the disadvantages of the classical ureterosigmoidostomy and reduces the number of postoperative febrile urinary tract infections as well to improve the continence rates Fisch and Hohenfellner introduced the rectum-sigma pouch (Mainz Pouch II), which transformed the high-pressure segment of the rectosigmoid into a low-pressure reservoir by detubularization and reconfiguration (76). As this diversion is used mostly in children and adolescents after failure of previous operations, the ureters are usually dilated. They can be safely re-implanted using a seromuscular extramural tunnel according to the procedure of Abol-Enein (77, 78).

In patients with an irreparable urethral sphincter defect and a small bladder capacity or even almost no bladder volume at all (e.g., after failure of primary bladder closure in patients with bladder exstrophy or incontinent epispadias) or in those in which the bladder must be removed (e.g., due to malignancies) a continent anal diversion using the seromuscular extramural tunnel technique for ureteral re-implantation can be offered. Basic prerequisite is a normal renal function, a competent anal sphincter and no previous or planned radiation of the small pelvis.

## CONTINENT CUTANEOUS URINARY RESERVOIRS

After a functional or anatomical bladder loss, in patients with incompetent anal sphincter or if an anal urinary diversion is not desired, a continent cutaneous urinary diversion is an option. Beside a normal or almost normal renal function, the will to self-catheterization is an absolute precondition. The patient and/or the parents must be able to perform the CISC/ CIC. Furthermore, a continent cutaneous urinary reservoir can be applied in preparation for a kidney transplantation (79).

After the first reports about the use of the cecum with the appendix as a stoma for continent cutaneous urinary diversion in the beginning of the last century (80, 81), the idea of a continent cutaneous urinary diversion was re-discovered in the 1950s by Gilchrist and his co-workers (82, 83). Nils Kock introduced the principle of detubularization and reconfiguration of intestinal segments for continent cutaneous urinary diversion (84). This method led to the development of various forms of continent cutaneous urinary diversion (85–89). The MAINZ Pouch as mixed Augmentation of Ileum and Coecum uses either the submucosally embedded appendix vermiformis (27, 90) or an ileal invagination nipple with fixation in the ileocecal valve as the continence mechanism (91). The continent stoma is attached to the umbilical funnel or to the lower right abdominal wall and offers good cosmetic and functional results.

Specific complications in continent cutaneous urinary reservoirs involve the continence mechanism, the pouch and the ureteral reimplantation. For the continence mechanism three different principles have been used so far. First of all, the "flap-valve" principle and its modifications are the most commonly used techniques. Better known as the flap-valve technique under the term "Mitrofanoff" stoma, which was first described by Verhoogen in 1908 and popularized by Paul Mitrofanoff in 1980 (20, 80). The technique of Yang-Monti, is used, if the appendix is already removed or too short or obliterated (92–94). In the long-term (7.7 years), it has been shown that the complication rate of the Yang-Monti technique is significantly higher compared to the use of the appendix (95). Other authors failed to confirm the higher complication rate with a slightly shorter follow-up (5.8 years) (96). Another option is the plication of the terminal ileal segment as it is used in the Indiana pouch (87). Ardelt and coworkers demonstrated in their review, that, on average, 87% of patients are continent when using the flap-valve principle. Problems with the catheterization occurred in about 20%. Stomal stenoses are a major problem in more than half of the patients (97). The relatively high rate of easy-to-treat complications seems to be the price for a good continent stoma (98).

Secondary, the principle of "Nipple Valve" goes back to studies of Watsuji and Perl (99, 100). Kock was the first to use the "Nipple Valve"-principle in the Ileum Pouch (Kock Pouch) (84, 101). It turned out, however, that the construction is quite complicated.

After a median follow-up of "only" 6.5 years, Abd-el-Gawad et al. reported pouch-related complications in 10 out of 13 children and 3 out of 7 adolescents (102, 103). If the principle is transferred to the ileocecal pouch and the invaginated nipple which is additionally fixed in the ileocecal valve, the complication rate is reduced (91). Wiesner et al. showed that ∼8–10% of the patients need a revision due to stomal incontinence and 15–20% developed a stomal stenosis in the long run. This was significantly less compared to the use of the appendix (104). This may be due to the larger diameter of the stoma. In their meta-analysis, Ardelt et al. showed that continence rates are comparable to those of flap-valve mechanisms (∼87%), fewer catheterization problems, and significantly lower rates of revision (97). Thirdly, hydraulic valves have not been proven to be useful in the long run (97, 105, 106).

Beside stomal stenosis, stone formation in the reservoir is one of the most common complications in children and young adults. For example, 15% of children and adolescents who have an ileocecal pouch (MAINZ pouch) due to a neurogenic bladder developed stones within the pouch after a moderate follow-up of 8.7 years (107). After performing a Kock pouch, the incidence rises to more than 40% (108). Regular and generous irrigation of the pouch can probably reduce the rate of stones (109). The third most common pouch-related complication is the development of a stenosis at the ureteral re-implantation site. Somani and coworkers demonstrated in their meta-analysis, that there is an incidence of implantation stenosis in these patients between 5 and 11% (110). Severely dilated ureters have even a higher risk of obstruction. In these patients the ureteral implantation technique of Abol Enein seems to be of advantage (111, 112). After a mean follow-up of 8.7 years, in 65 children and adolescents with 118 renal unit 16% of the submucosally implanted ureters had a ureteral stenosis and only 3% of the ureters implanted after the technique of Aboul Enein. At the last follow-up, 96% of the renal units showed in the ultrasound a reduced or a stable dilatation of the upper urinary tract (107).

If bladder augmentation with or without bladder outlet procedure is no option, the creation of a continent cutaneous urinary diversion is definitely an option in those patients who are able and willing to perform CISC. The relatively high complication rates of these complex procedures concerning the stoma, the reservoir, and the ureteral implantation site needs to be considered. These procedures should be only performed in centers of expertise for urinary diversions.

## INCONTINENT URINARY DIVERSION

Incontinent urinary diversion should be considered in patients who are not willing or unable to perform a CIC as well as patients with upper tract deterioration. Furthermore, those with an impaired renal function, who are not ready or suitable for a renal transplantation. Especially in those patients with a low or almost no compliance to CIC and/or medical therapy, a conduit is a temporary or a permanent solution. In children and adolescents, the colonic conduit has been shown to have less complications compared to the ileal conduit (113–124).

## FOLLOW-UP

In addition to the urinary diversion-related complications mentioned above, the use of bowel segments for urinary diversion may also result in metabolic changes. This is due to the incorporation of intestinal segments into the urinary tract (19). Therefore, lifelong regular follow-up is required. In this case, the upper urinary tract must be monitored by means of ultrasound and, if necessary, MAG-III clearance (assessment of bilateral renal function and exclusion of any urodynamically relevant urinary tract dilatation). Stones in the reservoir can be detected by ultrasound. Regular follow-up visits should be used to detect and treat urinary obstruction or small pouch stones at an early stage. When intestinal segments are incorporated into the urinary tract reconstruction, this absorption surface is lost to the physiological function of the gastrointestinal tract. The intestinal tract contains intrinsic absorptive and secretive properties that remain even after incorporation into the urinary tract (19, 125). A decreased absorption of vitamin $B_{12}$ from the small intestine or a decreased reabsorption of bile acids in the small intestine as well as in the large intestine can result (19). A variety of factors determine the extent of metabolic changes: length and type of intestinal segments used for reconstruction, atrophy of the intestinal mucosa as a result of chronic urinary diversion, renal and hepatic function, patient's age, previous radiotherapy or chemotherapy, and co-morbidities of the patient (125). Changes in the acid-base or electrolyte balance occur more often after continent urinary diversion due to the longer time the urine remains in the reservoir as well as the significantly larger absorptive surface. The variations depend on the type of bowel segment used (19). The risk of developing secondary malignancies seems to be lower in continent cutaneous and orthotopic urinary diversion than in anal urinary diversion (126). Higuchi et al. showed that the incidence of bladder cancer was not significantly increased in patients after ileum or colon bladder augmentation compared to a control group (4.6 vs. 2.6%). However, immunosuppression, transplantation and smoking do appear to confer an increased risk of malignancy in the setting of the augmented bladder (127). Even at low incidence, lifelong follow-up is essential. Especially after an anal urinary diversion, a regular endoscopic examination should be performed starting the 10th postoperative year.

## CONCLUSION

Nowadays, bowel segments can be used safely for urinary tract reconstruction. The operative decision should be in alignment with the patient's clinical condition as well as the individual's informed choice after all options have been thoroughly presented. These complex operations should be performed in high volume institutions/ centers of expertise who could deal with the possible complication and guarantee a life-long follow-up.

## AUTHOR CONTRIBUTIONS

RS, KZ, and NH writing and editing the manuscript.

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REVIEW
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# Update on Surgical Management of Pediatric Urolithiasis

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Urolithiasis has always been a fascinating disease, even more so in children. There are many intriguing facets to this pathology. This article is a nonsystematic review to provide an update on the surgical management of pediatric urolithiasis. It highlights the pros and cons of various minimally invasive surgical options such as extracorporeal shockwave lithotripsy (ESWL), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL), laparoscopy, and robotics. This article also describes the various intracorporeal disintegration technologies available to fragment the stone, including the newer advancements in laser technology. It also emphasizes the cost considerations especially with reference to the emerging economies. Thus, this manuscript guides how to select the least-invasive option for an individual patient, considering age and gender; stone size, location, and composition; and facilities and expertise available.

**Keywords: urolithiasis, minimally invasive surgery, extracorporeal shockwave lithotripsy, endoscopic intracorporeal lithotripsy, retrograde intrarenal surgery, percutaneous nephrolithotomy, robotics, pediatric urolithiasis**

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## INTRODUCTION

Urolithiasis is still intriguing due to its mysterious and complex nature, although being known to mankind from before the Christian era. Urolithiasis presents in all age groups including children from the neonatal period onward and may even be picked up on prenatal ultrasound (1). Apart from a high prevalence of pediatric urolithiasis in endemic areas (2, 3), there is an increasing incidence all over the world (4). Within the pediatric age group, clinical presentations are varied, and evaluation, including imaging, and management have to be modified depending on whether they are infants, preschool children, or pre- or post-pubertal teenagers (2, 5–7).

Pediatric patients carry a high probability of recurrence (8), and therefore, every effort should be made to prevent stone recurrence by ensuring complete stone clearance (9). This is a greater challenge with minimally invasive surgery (MIS) and limits the applicability of extracorporeal lithotripsy. Risk factors need to be identified, and these may be anatomical or metabolic, which require evaluation by dietary, urinary, and stone composition analyses (6, 10–14).

Historically, all stones are treated by open surgery (15–17). Currently, with the advent of MIS, the majority of the stones are managed by MIS utilizing extracorporeal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and ureteroscopy/retrograde intrarenal surgery (URS/RIRS) (2, 18, 19). Undertaking MIS in small children is challenging (20), which to a certain extent has been overcome by improvement in technology by the development of miniaturized instruments, which are referred to appropriately as Miniperc or Microperc (21–28). Sophisticated fine-caliber rigid and flexible ureteroscopes with improved optics are now available (29), which together with the development of high-power laser disintegration technology (30–32) and fine retrieval instruments such as nitinol baskets and graspers (33) have revolutionized MIS in children.

There are many facets to urolithiasis. In this review article, we will focus on the current status of the surgical management options available and attempt to guide the reader how to choose the best option considering the age, gender, stone size, location, and composition; the available expertise and facilities; considerations of cost; and both the surgeon's and patient's preferences.

## METHODS

For this nonsystematic review, a comprehensive search of the PubMed database was performed. This literature review is a survey focused on recent articles on surgical management of pediatric urolithiasis, which included the following key words; ESWL, PCNL, MiniPerc, MicroPerc, URS, RIRS, laparoscopy, and robotics in pediatric urolithiasis. This will also include our experience of surgical management of pediatric urolithiasis for the last two decades.

## EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY

Since 1986, when ESWL was first described, it remains the first-line of treatment of renal stones in children (34). However, its scope is now being challenged for the reasons that there have not been any major improvements in ESWL technology to improve the ESWL outcome of renal stone management, and it has largely failed to keep pace and compete with the better outcomes now being reported from the newer MIS developments such as RIRS and mini/micro PCNL.

### Technical Aspects of ESWL

The fundamental prerequisite for a successful ESWL is that the shockwaves can pass into the body and hit the stone with minimal loss of energy. In contrast to the pioneer lithotripter HM3 (with water bath), the later lithotripters have a gap between the shockwave source (therapy head) and the body that has to be bridged with a liquid transmission medium (usually an ultrasound gel) without any trapped air bubbles.

Devices using video cameras have been developed to check if the transmission zone is free of air bubbles and coupling is optimal (35). This equipment has been recently incorporated in the therapy head of some lithotripters with obvious advantage.

Another improvement has been the improved identification of the target and maintenance of an optimal position of the patient throughout the procedure by the use of continuous fluoroscopy or real-time ultrasound with lower radiation exposure (36).

ESWL in children are already being performed under general anesthesia, and therefore, high-frequency shallow ventilation may be used to reduce the range of respiratory movement and consequently increase the hit rate.

The risks of tissue injuries and subsequent bleeding can be reduced by inducing vasoconstriction by starting ESWL treatment with a series of shockwaves at a low energy level, followed by a pause or continuing with the low-power shockwaves for a longer period but incorporating a stepwise increase in the power. This treatment modality is termed as *ramping*. Ramping has many other advantages such as identifying the minimum energy level at which a stone starts to disintegrate, maintaining an optimum energy level which overcomes the attractive forces between the stone crystals, and avoiding overtreatment in terms of the energy level deployed. Several studies have shown that ramping results in better disintegration than when power is rapidly increased to high levels or when a high power level is used constantly during the treatment. High energy levels result in larger stone fragments with higher chances of ureteric obstruction, and low energy levels result in smaller fragments which are easy to pass (37, 38).

ESWL may be performed at various frequencies ranging from 30 to 120 shockwaves/min. On the basis of clinical and experimental studies, the recommended shockwave frequency for children is 60/min (1 Hz) (35).

### Complications of ESWL

#### Obstruction

The most frequent problem following ESWL is ureteric obstruction caused by impacted stone fragments. Its frequency increases with a large stone burden and when the stone is disintegrated into larger fragments. Steinstrasse is the commonest presentation where stone fragments accumulate in the distal ureter and cause severe obstruction. The reported incidence of abdominal colic is 6.29% and steinstrasse 6.0 and 8.5% (18, 39). This can be avoided by the placement of an internal stent preoperatively.

#### Infection

Urinary tract infection is another common complication which can occur secondary to infected urine or stone. This can be avoided by the use of preoperative antibiotics according to the culture and sensitivity reports and being insistent that preoperative urine cultures are confirmed as sterile.

#### Subcapsular Hematoma and Collateral Injury

Particular attention must be paid to the, fortunately, rare risk of renal subcapsular hematoma, renal parenchymal injuries, and injuries to the surrounding structures. One case of significant perirenal hematoma and one case of small asymptomatic subcapsular hematoma and skin bruising have been reported (40, 41). One of the major causes of subcapsular hematoma in children is the use of an excessive number of shockwaves and/or unnecessarily high energy levels in order to try to fragment the stone in a single session. It is always better to stop and re-treat. Successive ESWL sessions should have an interval of at least 10–14 days. Calcium channel blockers, various antioxidants, and free-radical scavengers have been used to decrease these injuries especially in retreatment cases (35).

To carry out lithotripsy in a safe and harmonious way, it is appropriate to avoid excessive numbers of shockwaves and high-risk energy levels. Considering these factors, repeated ESWL is not considered a failure but a simple consequence of the physics behind noninvasive stone disintegration (42–44). That may be true for adults where ESWL is mostly performed without general anesthesia and as an outpatient procedure. However, in children,

there is the additional factor that most ESWL are performed under general anesthesia (or sedoanalgesia in bigger children) in order to avoid apprehension, pain, and movement and to keep the stone under the shockwave target. In children, repeated ESWL carry a bigger burden which needs to be factored into the equation.

There is wide disparity in the stone free rates documented in the literature for ESWL in children ranging from 33 to 95% with incomplete information about the number of sessions (retreatment rates), residual fragments, and JJ stent placements. The results are incomparable not just for lack of information but also because of variability of the confounding factors like age, gender, the stone burden, location, composition, the type of lithotripter used, and the number of shockwaves in each session. All these factors impact ESWL outcome especially in children (39, 45–47).

## Stone Burden

Although staghorn stones (>3 cm) have been treated with ESWL, the retreatment rates are high, requiring up to five sessions (48). The European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) and American Urological Association (AUA) guidelines continue to recommend ESWL as the first line of treatment for renal stones <2 cm, but the retreatment rates could still be high (49) and nomograms reflecting this have been developed (50, 51). Our recommendation is to restrict the use of ESWL for renal stones up to 1.5 cm, except for lower calyceal stones when the upper limit should be 1 cm.

In our study of pediatric ESWL, the results showed an increase in the mean number of ESWL sessions with an increase in stone burden. In the single stone group of 158 renal units with a mean stone size of 10 ± 2.5 mm, 76% (121 renal units) were cleared in a single session, and 21 units were cleared in a second session, giving an overall clearance rate of 89% in a mean of 1.14 sessions. In the second group of 58 renal units comprising multiple stones having a mean size of 17 ± 5.3 mm, 46% (27 units) were cleared in a single session, 32% (19 units) were cleared in a second session, and 7% (4 units) cleared in a third session, giving an overall clearance rate of 86% in a mean of 1.54 sessions (5).

## Stone Location

Lower calyceal stones have a poorer clearance rate as compared to renal pelvic, upper, and mid calyceal stones (52). Lower calyceal stone clearance by ESWL is dependent on anatomical factors such as lower calyceal infundibular width, length, and infundibulopelvic angle (53, 54).

In our pediatric ESWL data, we reviewed the relationship between stone location and clearance, which showed that the best clearance rates following a single session of ESWL were for the upper calyx (87%) and pelvis (84%), and the poorest for the lower calyx (67%). The mean numbers of sessions required for clearance in the upper calyx, pelvis, and middle calyx were 1.1, 1.2, and 1.3, respectively, as compared to the figure for the lower calyx of 1.5(5).

## Stone Composition

Cystine and calcium oxalate monohydrate (COM) stones are hard, dense stones and difficult to fragment by ESWL, therefore resulting in poor stone clearance. One of the methods for the identification of the stone composition is by the attenuation value [in Hounsfield units (HU)] (55) on a noncontrast computed tomography scan (NCCT), which can easily differentiate between calcium ($HU > 1{,}000$) and noncalcium stones ($HU < 700$). However, it will require an NCCT in every patient and therefore increased radiation hazards. A crude way of identifying a calcium stone (COM) on an X-ray kidney, ureter, and bladder (KUB) is a densely radiopaque stone, which matches with the density of bone in a vertebral body, while the pure noncalcium stones (uric acid; xanthine; 2,8-dihydroxyadenine) are nonopaque. These are fragile and therefore easy to fragment with ESWL. A cystine stone is faintly opaque with a ground glass appearance. Struvite stones generally present as staghorn stones and are slightly less opaque. Although struvite are soft stones which are easy to fragment with ESWL, any residual fragment has a high affinity for rapid stone regrowth and recurrence (56).

In a small study of 58 renal units, we assessed the relationship between the stone densities in Hounsfield unit and the results of treatment by ESWL. The outcome showed that a lower HU is associated with better clearance for the same size of stone (5). Similar observations had been documented by others (57).

# ENDOSCOPIC INTRACORPOREAL LITHOTRIPSY DISINTEGRATION TECHNOLOGIES

The current technology of intracorporeal lithotripsy provides the urologist with several effective options for stone disintegration depending on the type of the endoscope used [ureterorenoscope (URS) or nephroscope, rigid or flexible] and the location and accessibility of the stone.

Four stone disintegration technologies are available for intracorporeal lithotripsy during endoscopic management of urolithiasis (58, 59). Each device has certain unique properties that make it more suitable for a particular application. Manufacturers' claims may contain elements of bias, and therefore, a thorough and impartial evaluation is important in order to be able to select the most appropriate device in any particular situation.

## Electrohydraulic Lithotripsy

Although electrohydraulic lithotripsy (EHL) is the least costly and can be used even with flexible 'scopes, it is relatively the most traumatic intracorporeal lithotripsy and is seldom used now.

## Ballistic Lithotripsy (Pneumatic Lithoclast)

Ballistic lithotripsy provides a durable, reusable, safe, and cost-effective means for stone fragmentation. It may be especially advantageous when large and hard stones are encountered. It can be used with scopes down to 10FG (Mini Perc) (21, 60, 61). Disadvantages could be a higher rate of stone repulsion, and it can only be used with rigid scopes.

### Ultrasonic Lithotripsy

It is safe, and although it may cause mucosal stripping, it does not create deeper perforations. For effective stone disintegration, it requires a relatively larger scope (>18FG) with a 4.5FG working channel to accommodate the hollow probe. It works best with standard PCNL for a large stone burden. It is less effective than pneumatic lithoclast (PL) for hard stones.

### Combination Devices

A PL combined with an ultrasonic beam aims to combine the advantages of both technologies. The superior, fast, coarse fragmentation ability of the pneumatic component is complemented by the simultaneous fine fragmentation and aspiration of the fragments via the hollow ultrasonic probe. Each modality can be activated separately or in unison. There are various types of the devices like Lithoclast Ultra (Boston Scientific, Natick, MAJ) and Cyber Wand (Olympus Surgical, Centre Valley, PA).

### Holmium: YAG Laser

This has brought great versatility to endoscopic intracorporeal lithotripsy (EIL) by introducing pulsed laser and allowing safe and effective stone fragmentation in the entire urinary tract. The laser output (power) can be adjusted by modulating the laser characteristics of energy (PE) and frequency (Fr). There are various generations of laser machines ranging from low power ($\leq$20 W) to high power (120 W). The later machines allow for much more adjustment in PE and Fr, thus allowing the stone to be disintegrated into fragments (high PE, low Fr) or converted into dust/powder (low PE, high Fr). The fragments can be removed by baskets, and dust/powder exits with the irrigation fluid without the need for retrieval devices.

Some newer machines also have the ability to change the pulse length and pulse duration or pulse width. In this way, the same amount of power (PE $\times$ Fr) can be delivered in ultra-short pulse (150 ms) to extreme long pulse (800 ms). It is being highlighted that the ultra-short pulse has the advantage of more ablative power, but the long pulse produces less fiber degradation and less retropulsion and produces smaller residual fragments and promotes a more dusting technique (30–32).

The new high-power (120 W) machines have evolved with some innovative integrated and modulated technological modes such as the "Moses effect" and the "burst mode." In the Moses effect, the laser pulse is divided into two phases; the first part divides the water between the laser fiber tip and stone, allowing the second part of the pulse to hit the stone unobstructed, thus being more ablative and less retropulsive (62). In the novel burst lasertripsy, each burst consists of three individual laser pulses having successively increasing pulse lengths, the first pulse being more energy intense while the last one is the least intense. It is suggested that the burst mode is significantly more ablative at similar power energy settings than the usual single pulse (63). Attempts are being made to incorporate a real-time stone/tissue differentiation capability using autofluorescence, thereby preventing the laser from firing against any structure other than the stone surface (64). Similar efforts are being made for the development of *in vivo* analysis of urinary stone composition (65). The manufacturers are trying hard to make a well-designed interface to make these holmium: YAG laser (Ho-YAG) laser lithotripters user-friendly.

Thulium laser technology has evolved and is gaining attention now that it is capable of pulsed emission. In comparison to Ho-YAG lithotripsy, it is two to four times faster and produces minimal or no retropulsion without any significant heat production. Therefore, pulsed thulium laser appears to have promising prospects (66).

## RETROGRADE INTRARENAL SURGERY

Since the development of sophisticated, miniaturized, and actively deflectable flexible ureterorenoscope (FLURS) with excellent optics and Ho-YAG lasers, RIRS has become a popular modality to treat upper ureteric and renal stones $\leq$2 cm (26, 67, 67, 68). FLURS with greater flexibility, maneuverability, secondary deflection capability, and wide range of deflection allows better treatment and access to lower pole urolithiasis (69, 70). However, in some cases, especially in younger children, it may be relatively difficult because of compromised deflection in renal pelvis. Stones > 2 cm and staghorn stones confer a high risk for treatment failure, illustrating that stone location and stone burden are the most important risk factors for treatment failure in RIRS as well.

A randomized trial comparing the outcomes of RIRS and mini PCNL in pediatric patients with stones >2 cm revealed that the success rate was significantly higher for mini PCNL with figures of 71 and 95%, respectively (60).

One of the advantages of RIRS is that urologists are used to performing procedures through the natural route of the urinary tract, which results in a short learning curve. RIRS is less invasive than PCNL and is therefore the most preferred approach to treat renal calculi in patients with a bleeding diathesis.

However, there are certain limitations with RIRS, especially in small children. The majority of the RIRS series, especially where the results are compared with PCNL, are biased by the fact that the children treated by RIRS are somewhat older and the stone burden is generally less than the PCNL groups (61, 71–74). A recent systematic review of children undergoing RIRS reported an aggregated success rate of 87.5% and a complication rate of 10.5%. However, the younger children had a much higher risk of complications (24%) compared with the older children (7%) (75). This clearly indicates that RIRS should be recommended with caution in younger children.

Children have narrow caliber ureters, and access is difficult or impossible without active dilatation with a balloon or preferably by inducing passive dilatation with prestenting. Concerns about ureteral ischemia, perforation, stricture formation, and vesicoureteric reflux as a result of dilating small caliber ureteric orifice are well recognized (76, 77). Although some studies do report access without prestenting in up to 60% of cases, active ureteral dilatation with 8–10 coaxial dilators were used in 97% of these cases. In the remaining 40% with failure to access, the pediatric ureter remains narrow and inaccessible for the URS at the ureteral orifice, the iliac vessels, or the uretereopelvic

junction. Therefore, passive dilatation with prestenting was undertaken (77). It is also documented that prestenting does allow for more reliable access to the ureter and a shorter operative time.

Active or passive ureteric dilatation is also needed for the majority of the procedures, which required the placement of a 9/11FG ureteric access sheath (UAS). The UAS is placed to allow the FLURS to be removed and reintroduced repeatedly, allowing dust and fragments to clear and maintain good vision. The UAS also allows irrigation fluid to flow easily and so maintains a low intrarenal pressure, thereby decreasing the chances of pyelovenous and pyelolymphatic backflow and reducing the chances of developing sepsis.

UAS carries the risk of ureteric injury ranging from minimum mucosal damage to major lacerations, stricture, and avulsion (76). Therefore, almost all cases require post RIRS JJ stent placement for 2 weeks in order to allow the ureteric damage to heal. The majority of the series of RIRS in children which document the outcome from a single operative session do not take into consideration the anesthesia required for prestenting to provide passive ureteral dilatation. Similarly, since the majority of cases require postoperative stenting, especially where an UAS was used, they will require another anesthesia session for stent removal. Therefore, the outcome of RIRS in these patients is really that of a staged procedure requiring two to three general anesthetics and is not really a genuine single session.

## Ureterorenoscopes

URS is the treatment of choice for calculi, particularly in the distal and mid ureter and is more efficient than ESWL (78). Semi-rigid URS of size 4.5/6, 6/7.5, and 8/9.8FG are used depending on the age and anatomy of the patient and the size and location of the stone, as well as considering the technical requirements. The semirigid URS are more durable and have better visibility, faster irrigation flow, and larger working channels than the fully flexible models, and therefore, it is possible to access the whole ureter, even as far as the pelvicalyceal system. However, the ability of the 'scope to bend is limited, and, especially with large psoas muscles, access to the upper ureter may be difficult in comparison with flexible URS. Therefore, semirigid URS may not be the first choice for the proximal ureteric stone (79).

The deflectable tip of the flexible 'scopes is more suitable for a tortuous ureter and for upper ureteric stones, which often migrate into the kidney. The flexible 'scope can follow the stones, and RIRS may be possible in the same session. The flexible ureteroscope permits only lasertripsy; they are costly and fragile, and therefore, the treatment with FLURS is much more expensive than with semirigid 'scopes.

Several studies have highlighted the fact that the flexible 'scope undergoes wear and tear and requires major repair after 14–32 RIRS sessions. Even without apportioning the high initial cost of the instrument, the maintenance and repair costs over each session of RIRS still make it a highly expensive treatment option (80, 81).

Lower ureteric stones are best managed by semirigid URSs by employing the PL or Ho-YAG laser (LL). The outcome in terms of stone clearance and complication rates is excellent and comparable. Although PL has the advantage of being significantly cheaper as compared to LL, PL can only be used through 6/7.5FG 'scopes and above, while LL can be used with the small 'scopes (4.5/6FG), which is an advantage for infants and small children (2, 5, 79, 82, 83).

Our results in 554 children with lower ureteric stones managed endoscopically using PL, low-power 30-watt Ho-YAG laser, or high-power 80-watt Ho-YAG laser performed between 2009 and 2016 with a comparable demography and stone burden showed excellent stone clearance rates of 91 vs. 89 vs. 95%, respectively ($p = 0.5$), with the number of sessions required showing no statistical difference between the three techniques. There was no difference in complications, which were Clavien I and II. However, it was recognized that the LL technique was costly.

Despite the minimally invasive nature of RIRS/URS, they are not without intraoperative and postoperative complications. A systematic review of 34 studies from 1996 to 2016 comprised of 2,758 children (2,994 procedures). A complication rate of 11.1% (327/2,994) was reported; 69% of these were Clavien grade I, and 31% were grade II/III. There were no Clavien grade IV and V complications (84). In another multicenter study of 642 children where semirigid ureterorenoscopy was performed for ureteric stones, a total of 54 (8.4%) complications have been documented where operative time was the only statistically significant parameter affecting the complication rate (78).

# PERCUTANEOUS NEPHROLITHOTOMY

## Patient Positioning

### Prone Position

Percutaneous Nephrolithotomy was conventionally performed in the prone position for historical reasons, being more familiar to the majority of urologists and for fear of splanchnic injury. It also gives a wide operative field for manipulation of instruments and the possibility of access through multiple calyces (85, 86). Prone PCNL has certain limitations such as difficulty for the anesthetist with regard to control of the endotracheal tube and freedom of ventilation. Resuscitation is extremely difficult if an emergency such as cardiac arrest occurs during the procedure (87).

### Supine Position

The first supine PCNL was performed in an adult by Valdivia-Uria in 1987 (88). Since then, many modifications of the supine position have been introduced to widen the operative field and increase maneuverability of the instruments, which were limitations of the original Valdivia-Uria supine position. Apart from that, most urologists were not familiar with the supine PCNL position. In most cases, the only access site available is the lower calyx, and there is hypermobility of the kidney, which needs to be controlled. There are number of potential advantages of supine pediatric PCNL. It is comfortable for the surgeon as he is working in a sitting position and it counters the anesthetic limitations inherent in the prone position.

In supine PCNL, the tract is horizontal or with a slight upward inclination in relation to the operative table, which allows

most irrigation fluid and stone fragments to fall away from the patient, thus decreasing the risk of hypothermia and ensures a low pressure in the pelvicalyceal system, which results in a decreasing incidence of sepsis and better stone-free rates with fewer residual fragments. The operative time is usually shorter as time is saved by avoiding the need to change position following induction and quick clearance of the stone fragments (85, 89). A simultaneous endoscopic combined intrarenal surgery (ECIRS) can be performed particularly when the stone fragments are inaccessible with PCNL (90).

### Lateral Position

Percutaneous Nephrolithotomy in a lateral position was first performed in a morbidly obese patient in 1994. Later on, more studies described the anesthetic advantages of lateral PCNL in the morbidly obese or kyphotic patients and patients with severe medical risk factors and comorbidities. They also describe the advantage of being able to rotate the C-arm fluoroscope to obtain an anteroposterior projection and perform nephroscopy simultaneously. Lateral PCNL has also been performed with ultrasound-guided renal access to reduce the radiation dose. The effectiveness of stone clearance in lateral PCNL lies in good ergonomics. The position of the pelvicalyceal system relative to the calyx enables gravity-assisted migration of calculous fragments from the calyces to the pelvis for easy removal. Conversely, there is a higher likelihood of stone fragment migration into the ureter, which may require preprocedural stenting or postprocedure ureterorenoscopy to remove the remaining ureteric stones. A number of other lateral PCNL techniques have been proposed, including the split leg modified lateral technique (85, 91). The operating time, stone clearance rates, and safety of lateral PCNL are comparable to those of prone and supine PCNL, but one of the disadvantages of lateral PCNL is that synchronous bilateral PCNL is impossible (85, 91).

## "Standard to Mini PCNL: How Small One Should Go?"

Classical (standard) PCNL in children required a 30FG Amplatz sheath and employed a 24FG nephroscope. The advantage of such generous access was very high (>90%) stone clearance rates in a single session but was not easily applicable in small children, where there was the risk of renal damage or excessive bleeding requiring blood transfusion.

The miniaturization of equipment for PCNL in pediatric patients has facilitated its use in all age groups and has also provided an opportunity to treat smaller stones that would otherwise be candidates for ESWL or RIRS. PCNL remains the gold standard treatment for large renal stone >2 cm and complex stones (49, 74).

Retrospective comparative studies have indicated that mini PCNL provides at least similar stone-free rate for moderate-size stones in comparison to RIRS (61). ElSheemy et al. also demonstrated superior results with mini PCNL (14FG) for renal calculi of 10–25 mm in preschool children in comparison to ESWL with comparable complication rates but a longer hospital stay (52).

In a large retrospective multi-institutional cohort including 1,205 pediatric renal units who underwent PCNL, the use of a sheath size >20FG was an independent predictor of complications and bleeding necessitating transfusion (92), and the association between a larger tract and greater blood loss has been confirmed in several other reports (25, 93, 94). Consistent with these reports, it was demonstrated that PCNL with a smaller tract <24FG results in lower blood loss without a decrease in success rate (18).

Similarly, in our study of 1,135 renal units, we have also observed that blood transfusion requirement was significantly less in all age groups when <20FG sheath was used. Blood transfusion rate was higher in children with larger stone burdens and in younger children with lower allowable blood loss (2).

The other important factors to prevent bleeding are an understanding of the pelvicalyceal and intrarenal vascular anatomy and the skilled application of a proper technique. The selection of the puncture site should be according to the stone location. The puncture is performed through the fornix, in the direction of the infundibulum to avoid trauma to the blood vessels adjacent to the infundibulum. In addition, while manipulating the nephroscope during stone fragmentation and retrieval, it is important to avoid excessive torque and the creation of false passages which traumatize the parenchyma.

There is still no strict standardized nomenclature for PCNL. Various classifications have been proposed and published in the literature, which include standard/conventional PCNL (22–30 FG), mini PCNL (11–22 FG), minimally invasive PCNL (MIP) (9.5–26 FG), Chinese mini PCNL (14–20 FG), ultra mini PCNL (11–13 FG), micro PCNL (4.8 FG), mini micro PCNL (8 FG), and super mini PCNL (10–14 FG). The first documented mini PCNL was by Jackman using an 11 FG peel away vascular access kit (95). Since then with the growing diversity of the miniaturized PCNL, the terminology mini PCNL has been loosely used for tract size 11–22 FG, and thus, mini PCNL is poorly defined (96–100).

We also initially started off with adult-sized nephroscopes (27 and 24FG) and gradually reduced it to 20, 18, and 15FG. Currently, we routinely use mini PCNL utilizing a 12FG nephroscope with a straight channel and offset lens or a 9.8FG cystoscope through a 16FG working sheath in most situations (2).

We occasionally employ rigid pediatric cystoscopes 6/7.5–10.5FG through a 12FG Amplatz sheath. These may be called an ultra mini PCNL. These scopes are readily available in most pediatric urology units and are sturdy, rigid, and reusable and, therefore, cost-effective. These 'scopes have an added advantage for use in the narrow and difficult anatomy of small children and could be an economic compromise to microperc.

## Microperc

The term microperc refers to a system in which the telescope, working channel, and irrigation are combined in a needle, which can be as small as 4.8FG and requires only a single puncture, thereby avoiding the need for tract dilatation (101). The main advantage of microperc in children is to minimalize bleeding.

The technique may only be used in very selected cases, but it allows direct puncture into the relevant calyx via the all-seeing needle and direct fragmentation/powdering of the stone

*in situ*. With no need for tract dilatation, less radiation exposure, and, consequently, less operating time, it should result in lower complication rates.

There are certain limitations of the microperc; first, the vision gets compromised more quickly with the slightest bleeding and stone dust. The vision may not be as good as in mini PCNL because the irrigation fluid is pushed intermittently, and there is no regular outflow passage. Necessary precautions should be taken to control the intrarenal pelvic pressure at every step of the procedure by placing a large caliber ureteric catheter in the renal pelvis, and saline irrigation should be carefully monitored during the procedure. It has been demonstrated that the intrarenal pressure is significantly higher in the micro PCNL compared to the standard PCNL (102).

Secondly, if the stone fragments migrate into a different calyx, it becomes impossible or difficult to access them. Thirdly, microperc instruments are costly and meant to be disposable (98), making their universal use in emerging economies, where much of the stone burden in children lies, extremely difficult.

The use of very small tracts has to be individualized on the basis of stone location and burden and balanced against the limitation of low irrigation fluid flow, impaired visualization, and limitation in the use of disintegration technology and grasping forceps.

The complications of PCNL in children have been reported from 9 to 27.7% (92, 97). Studies on micro PCNL (tract size <10 FG) reported a complication rate of 9% with a higher incidence of renal colic. Studies on ultra mini PCNL (tract size 10–14 FG) reported 14% complications with higher incidence of hematuria, renal extravasation, or renal pelvic perforation. A multi-institutional study of 1,157 children treated with PCNL (nephroscope 17 FG to 26 FG and URS 9.5 FG) reported a complication rate of 27.7%, where 7.7% were intraoperative and 20% were postoperative complications. The majority of the complications were Clavien grade I and II, and there were no grade IV and V complications (92, 97). Most of the series have limited numbers; therefore, risk factor analysis is difficult.

### Overview

One of the approaches to PCNL may be to start with a small caliber tract and, if needed, depending on the stone burden and its response to disintegration, then under direct vision to undertake progressive dilatation, keeping the risks of bleeding as low as possible. Alternatively, two or multiple smaller tracts may be established in order to achieve complete stone clearance if the stones are in places which are difficult/impossible to reach through the primary tract. In situations where the rigid instruments fail, the flexible nephroscope can be deployed in conjunction with lasertripsy.

The truism remains that one should try to keep the tract as small as possible but make it as big as needed.

## ENDOSCOPIC COMBINED INTRARENAL SURGERY

This is a combined procedure where both RIRS and PCNL are performed simultaneously by two surgeons working together. It may be performed either in the supine or prone position, but it is a situation where experience in supine PCNL clearly has benefits. ECIRS is usually recommended for complete clearance of a large stone bulk, such as a staghorn calculus and for multiple stones located in difficult anatomical positions. Such complex stones cannot be cleared either by RIRS or PCNL alone in a single session. It also reduces the operating time. The most appropriate renal puncture and the PCNL tract can be acquired easily with the assistance of ureterorenoscopy and especially if combined with ultrasound (103). There are still limited data on the outcomes of ECIRS in children (22, 104).

## LAPAROSCOPIC AND ROBOTIC SURGERY

### Pyelolithotomy and Nephrolithotomy

With the advent of newer MIS modalities, the role of open surgery for urolithiasis has been minimized. With the increasing use of robotic surgery in pediatric urology, these approaches are being revisited. Laparoscopic and robotic-assisted pyelolithotomy (RPL) or nephrolithotomy (RPNL) or ureterolithotomy should not be the initial treatment choice for renal or ureteric stones. However, in selected patients, it can be a reasonable and safe minimally invasive surgical option even in children. Compared with a pure laparoscopic approach, robotic-assisted laparoscopic surgery has the advantages of improved dexterity for suturing and reconstruction (105, 106). It can be performed retroperitoneally; however, the transperitoneal approach is preferred by most surgeons. Compared to other endourological options, it has certain advantages of complete stone removal without fragmentation, thereby increasing the chances for complete stone clearance up to 96% in one procedure, especially when a single stone is present (107–110). It may prove particularly relevant for larger stones where the chances of residual fragments are high with other endoscopic procedures such as PCNL or RIRS. It has a significantly lower rate of bleeding and sepsis as has been shown in meta-analysis (111). Robotic pyelolithotomy and nephrolithotomy may be recommended in urolithiasis with concurrent pelvi-ureteric junction obstruction, where simultaneous reconstruction and repair are required. There are many unusual and difficult circumstances which may also prove amenable to the robotic-assisted approach (112):

- A very large stone burden, such as complete or partial staghorn calculi
- Stones containing gas
- A stone in a calyceal diverticulum
- Stones in ectopic kidneys
- Stones with complex urinary tracts with unfavorable collecting systems
- Failed previous endourological procedures
- Complex stones (especially very hard stones which are difficult to fragment) where multiple tracts for PCNL might otherwise be needed.

In practice, the majority of cases that are managed by pyelolithotomy are those having a single large stone in an extrarenal pelvis, which may be removed completely without transgressing the parenchyma with its attendant risks. Others may be managed by extended pyelolithotomy or the use

of pyeloscopy using a flexible nephroscope through one of the abdominal ports and employing graspers or laser dusting. For some patients, dissection of the renal pelvis can be extremely challenging as the pelvis may be inflamed with adherent fat, making demarcation of planes difficult and bloody.

In cases of calyceal diverticulum and peripherally located calyceal stones where access to the collecting system through the renal pelvis is difficult, nephrolithotomy may be performed directly in the thinnest part of the parenchyma with minimal bleeding and without any vascular clamping. An intraoperative ultrasound probe may be used to locate the stone and plan the incision (113). At the moment, the use of robotic surgery is determined by availability of the robotic armamentarium, individual skills, logistics, and, especially, the cost constraints. There is a lack of available data especially in pediatrics as the majority of the experience to date is in adults and retrospective. However, it is quite possible that future generations will be more comfortable and have more access to robotic surgery than is generally the case in most pediatric urology units today.

## VESICAL STONES

Most vesical stones can be managed endoscopically via the urethra [perurethral cystolithotripsy (PUCL)] and percutaneous cystolithotripsy [percutaneous (suprapubic) cystolithotripsy (PCCL)] (114).

### Perurethral Cystolithotripsy

The miniaturization of cystoscopes and URSs has made it possible to manage bladder stones up to 2 cm transurethrally with 100% clearance and minimum complications. Pneumatic (mechanical) lithoclast is a cost-effective technology and can safely be used through a 7 or 8 FG URS (115). Lasers are costly and take longer to disintegrate the same-sized stone; however, they can be used through the fine caliber miniscope and can thus be very safely used in babies <1 year of age. Postoperatively, relief of symptoms, attainment of normal voiding, and a normal pre- and post-void ultrasound of the bladder confirm a successful outcome.

### Percutaneous (Suprapubic) Cystolithotripsy

PCCL has gained popularity as a quick and safe minimally invasive procedure, especially for large stones between 2 and 3.5 cm, and even in smaller stones, PCCL is applicable where there is limited or no urethral access and management is difficult transurethrally with risks of failure, long anesthesia and surgical time, and urethral injury. PCCL has a low morbidity and complication

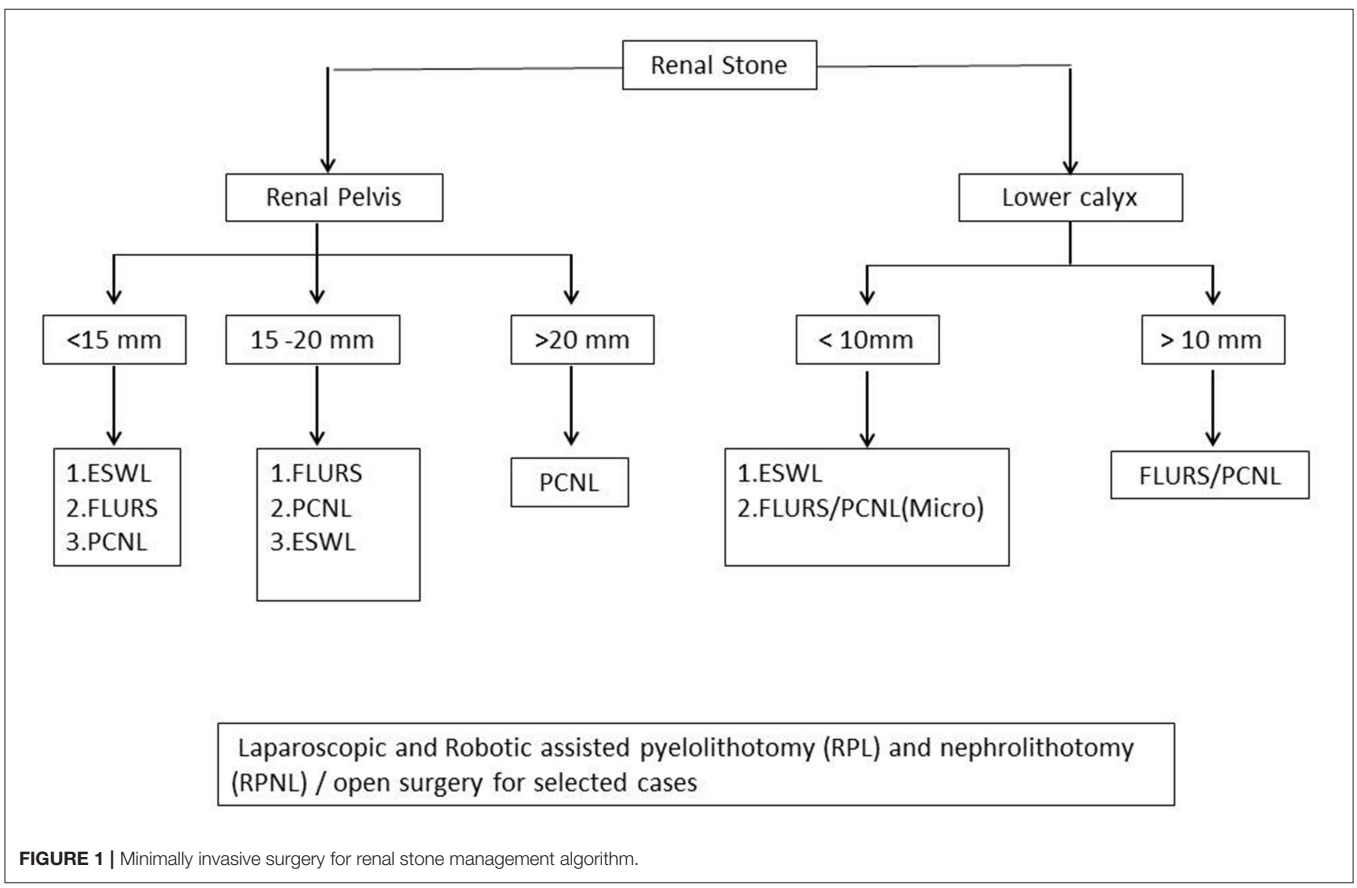


**FIGURE 1 |** Minimally invasive surgery for renal stone management algorithm.

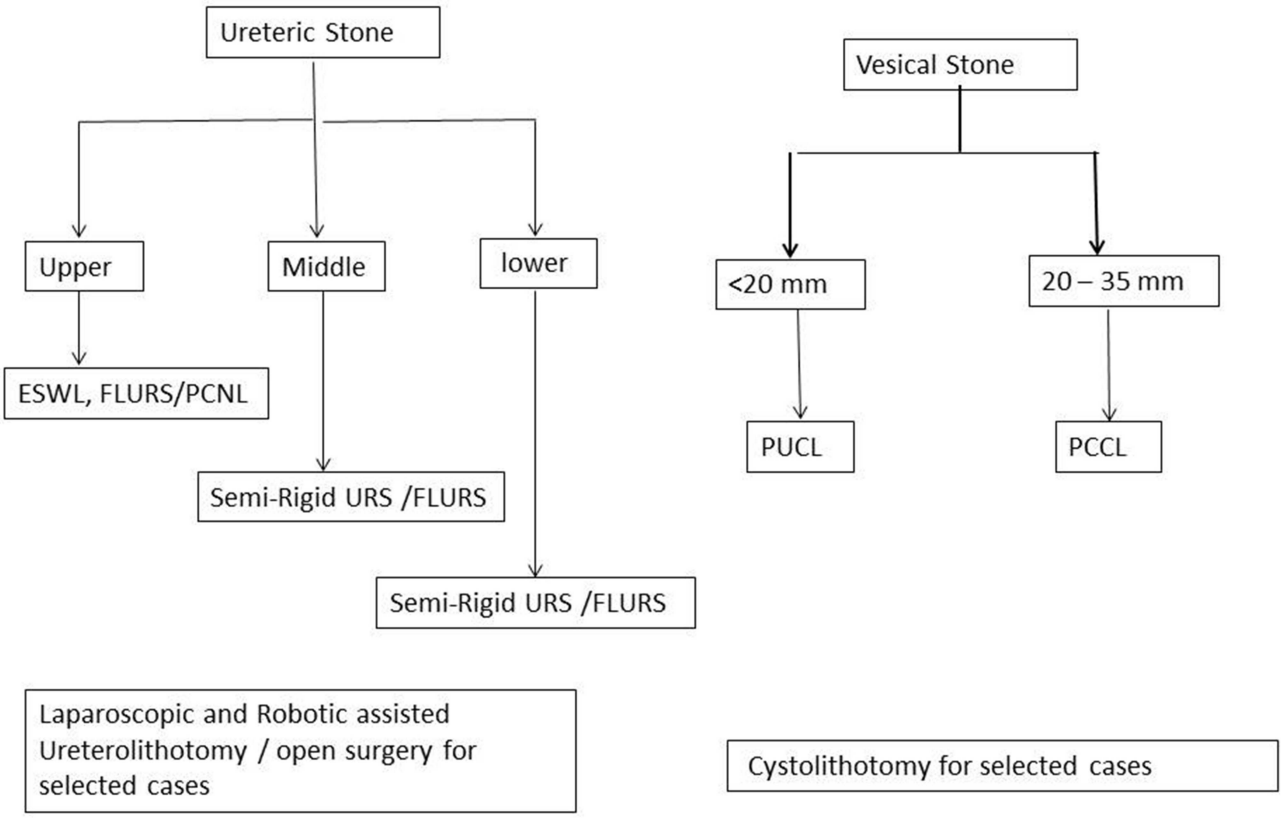


**FIGURE 2 |** Minimally invasive surgery for ureteric and vesical stone management algorithm.

rate, better cosmetic outcome, shorter hospital stay, and postoperative urethral catheterization compared with open cystolithotomy (116).

Note: Management algorithm for renal, ureteric, and vesical stones are presented in **Figures 1**, **2**.

## AUTHOR CONTRIBUTIONS

All authors contributed to the conception of this review. SS, SA, and BA conducted the review of the literature. SS and SA wrote the manuscript.

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REVIEW
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# Anterior Urethral Strictures in Children: Disease Etiology and Comparative Effectiveness of Endoscopic Treatment vs. Open Surgical Reconstruction

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Pediatric anterior urethral strictures are rare and recommendations regarding treatment strategies derive from small monocentric case series. In 2014, a collaborative effort of the Société Internationale d'Urologie and the International Consultation on Urological Diseases drafted the first systematic and evidence-based guideline for diagnosis and treatment of urethral strictures in children. Against this backdrop, we performed an updated literature review to provide a comprehensive summary of the available evidence and contemporary outcomes with a focus on comparative effectiveness of endoscopic treatment (dilation or urethrotomy) vs. open surgical reconstruction. Overall, 22 articles reporting on children with anterior urethral strictures were included into the review. Most strictures were iatrogenic (48%) and traumatic (34%), whereas congenital (13%), inflammatory (4%), or postinfectious strictures (1%) were rather rare. The cumulative success rate of endoscopic treatment and urethroplasty was 46% (range: 21–75; $N = 334$) and 84% (range: 25–100; $N = 347$), respectively. After stratifying patients according to urethroplasty technique, success rates were 82% (range: 25–100; $N = 206$) for excision and primary anastomosis, 94% (range: 75–100; $N = 40$) for graft augmentation, 97% (range: 87–100; $N = 30$) for flap urethroplasty, and 70% (one study; $N = 20$) for pull-through urethroplasty. In conclusion, endoscopic approaches are rather ineffective in the long-term and open surgical reconstruction via urethroplasty should be preferred to avoid multiple, repetitive interventions. Future research may involve multi-institutional, collaborative, and prospective studies, incorporating well-defined outcome criteria and assessing objective surgical endpoints as well as patient-reported functional outcomes.

**Keywords: endoscopy, iatrogenic disease, mouth mucosa, pediatrics, urethral stricture**

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## INTRODUCTION

Anatomic lower urinary obstruction is a rather rare problem in pediatric urology. Whereas, voiding difficulties are commonly diagnosed in boys with urethral valves or hypospadias, the experience in treatment of isolated pediatric anterior urethral strictures is remarkably scarce. Thus, information on pediatric or adolescent strictures is commonly extrapolated from the adult literature (1). With exception of the collaborative 2014 Société Internationale d'Urologie (SIU) and

International Consultation on Urological Diseases (ICUD) task force to generate evidence-based recommendations for those patients (2), there are literally no keystones to base evidence-based treatment considerations on. Given that urethral stricture disease is relatively rare in adults (3), the incidence in children is even smaller and there is a paucity of experience in patients up to 18 years. As a consequence, etiology and management in pediatric urethral stricture disease are not well defined. In this review, we aimed to provide a contemporary overview of available operative techniques, treatment approaches, and outcomes in this subgroup of patients.

## MATERIALS AND METHODS

We performed a literature review through PubMed for articles published between 2010 and September 2018 on urethral strictures in children using the search term "urethr* AND (child* OR ped*) AND stricture." Additionally, we included select evidence from the recent landmark reviews by Kaplan et al. (1, 2). We excluded articles, which reported on adult patients only, isolated posterior strictures given the entirely different etiology in most cases, or those without information on (standardized) outcomes. Of note, we also considered articles in which patients with strictures of the anterior urethra were pooled together with children suffering from posterior urethral strictures. Articles about re-operative surgery after previously failed hypospadias repair were excluded if neo-urethral strictures were not mentioned and described in detail, given that re-do hypospadias repairs may not generally implicate urethral stricture disease. We tabulated information on authors and year of each study, number of included patients, stricture etiology, location, and length, the surgical approach, age at surgery, the chosen definition of treatment success, success rates, length of follow-up, and the type of study design. Of note, we chose to summarize conservative success rates after the very initial treatment. We believe this is important to mention, given that some authors do report "overall" success rates derived from several subsequent treatment sessions (e.g., after multiple urethrotomies).

After applying selection criteria, 22 articles reporting data on 682 patients were included into analyses. Treatment approaches varied across the studies with seven articles reporting on urethrotomy or dilation (4–10), 11 articles reporting on urethroplasty (11–21), and four articles reporting on both techniques in comparative analyses (22–25). A summary of all articles considered for this review is depicted in **Tables 1**–**3**.

## STRICTURE ETIOLOGY AND LOCATION

According to the SIU/ICUD consultation on urethral stricture nomenclature (26), stricture etiology should be stratified into iatrogenic (e.g., hypospadias-associated, post-catheterization, etc.), traumatic, inflammatory (e.g., lichen sclerosus-associated), postinfectious, and congenital. Emphasis should be put on the term "congenital stricture," which is a less common subcategory, and the diagnosis should generally only be made in the absence of urethral manipulation, infection, inflammation or trauma (26). Accordingly, patients without evident etiology were classified as "congenital/unknown" within this review.

In all 682 patients, stricture etiology was mostly iatrogenic (48%), followed by traumatic (34%), and congenital (13%) strictures. Postinfectious (1%) and inflammatory strictures (4%) were rather rare (**Figure 1**). Given that this review aimed to focus on anterior stricture location, the majority of patients (62%) did present with an anterior urethral stricture, of which 45% had bulbar, 35% had penile, and 3% had bulbopenile strictures (**Figure 2**). In order not to omit data from studies reporting on outcomes in children with anterior and others with posterior strictures, we included those studies into the review. Thus, there were 25% of patients with posterior strictures and 13% in which the stricture location was not further specified (**Figure 2**).

## PRESENTATION AND PREOPERATIVE EVALUATION

Clinical symptoms of pediatric urethral strictures are heterogeneous and the diagnosis should be ruled out if no other underlying reason can be found. Children may present with hematuria, pain, nighttime and/or daytime wetting, urinary tract infections, decreased stream, high post-void residual volume, straining to void, or dysuria (2). According to the SIU/ICUD consultation, uroflowmetry cannot be relied upon to rule out a clinically relevant stricture, and thus, combined retrograde urethrography and voiding cystourethrography as well as endoscopy are recommended as reliable diagnostic procedures (2).

## ENDOSCOPIC TREATMENT

Overall, seven studies reported on outcomes after endoscopic treatment (urethrotomy or dilation) (4–10) and four studies reported on comparative outcomes following endoscopic treatment vs. urethroplasty (22–25) (**Tables 2**, **3**). Of note, only two articles performed a (partially) prospective data collection (4, 10) and thus, the level of evidence was low. The chosen definition of treatment success was heterogeneous, whereas most authors used the relatively easily assessable definition of asymptomatic voiding and no clinical symptoms (4, 5, 7, 8, 10, 23–25). Two studies did not define treatment success at all (6, 22), and seven articles chose radiographic evidence of urethral patency or no further need of any intervention as an adjunct definition of a successful surgery (4, 5, 8–10, 24, 25). The average cumulative success rate of urethrotomy or dilation in 334 patients (**Tables 2**, **3**) was 46% (range: 21–75). Follow-up intervals varied across the studies, ranging from a median follow-up of 11.5 months (6) to an average of roughly 6.5 years (7, 9, 23, 24) Some authors included patients undergoing different treatment approaches (cold knife and laser urethrotomy or dilation) into their analyses. There were only three studies with distinguishable outcomes after dilation: overall, 23 of 58 patients (40%) recurred at a follow-up of at least 12 months (5, 22, 25). In two studies, patients

**TABLE 1 |** Summary characteristics of included studies of patients who underwent urethroplasty for pediatric urethral stricture.

| Author | Year of study | Number of patients | Stricture etiology | Stricture location | Stricture length | Surgical approach | Age at surgery | Definition of treatment success | Success rate | Length of follow-up | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ashraf et al. (12) | 2018 | 5 | Inflammatory (*N* = 5) | Distal/Penile (*N* = 5) | Median 2.7 cm; Range: 1.5–4.0 | One-stage Asopa BMGU (*N* = 5) | Median: 14 years; Range: 11–18 | Functional success (i.e., improvement in uroflowmetry, patient satisfied with urinary stream) | 100% | Median: 34 months; Range: 30–42 | Retrospective |
| Aldaqadossi et al. (11) | 2018 | 23 | Iatrogenic (*N* = 16); Postinfectious (*N* = 4); Congenital/Unknown (*N* = 3) | Bulbar (*N* = 15); Bulbopenile (*N* = 8) | Mean: 5.1 ± 1.0 cm | Circular penile fasciocutaneous flap (*N* = 23) | Mean: 9.3 ± 2.6 years | Normal voiding, no radiographic manifestation of stricture, no further postoperative interventions | 87% | Mean: 52 ± 17 months | Retrospective |
| Djordjevic et al. (13) | 2011 | 15 | Iatrogenic (*N* = 15) | Penile (*N* = 15) | Mean: 2.6 cm; Range: 3.0–5.5 | One-stage ventral BMGU with tissue coverage and graft hanging (*N* = 15) | Mean: 13 years; Range: 9–17 | Adequate urethral diameter, confirmed by uroflowmetry and urethrography | 100% | Mean: 37 months; Range: 17–73 | Retrospective |
| Hafez et al. (14) | 2005 | 35 | Traumatic (*N* = 35) | Bulbar (*N* = 9); Bulbopenile (*N* = 2); Posterior (*N* = 24) | Mean: 2.6 cm; Range: 1–5 | EPA (*N* = 35) | Mean: 11.9 ± 3.4 years; Range: 6–18 | Asymptomatic voiding without clinical evidence of residual stricture (good flow rate and absence of residual urine) | 89% | Mean: 46 months; Range: 6–132 | Retrospective |
| Pfalzgraf et al. (15) | 2012 | 17 | Traumatic (*N* = 8); Iatrogenic (*N* = 7); Congenital/Unknown (*N* = 2) | Bulbar (*N* = 13); Penile (*N* = 1); Posterior (*N* = 3) | Mean: 2.5 cm; Range: 0.5–4.0 | EPA (*N* = 8); One-stage BMGU (*N* = 7); Staged BMGU (*N* = 2) | Median: 9 years; Range: 1–13 | No subsequent procedure required | 89% | Median: 30 months; Range: 4–115 | Retrospective |
| Rourke et al. (16) | 2003 | 17 | Traumatic (*N* = 12); Iatrogenic (*N* = 3); Congenital/Unknown (*N* = 2) | Bulbar (*N* = 8); Posterior (*N* = 8); Bulbopenile (*N* = 1) | Median: 2.2 cm; Range: 1.0–6.0 | EPA (*N* = 14); Penile flap augmentation (*N* = 2); One-stage BMGU (*N* = 1) | Median: 13.4 years; Range: 7–17 | Urinary continence with a patent urethra and absent lower urinary tract symptoms | 94% | Median: 57 months; Range: 12–124 | Retrospective |
| Shenfeld et al. (17) | 2008 | 14 | Traumatic (*N* = 9); Iatrogenic (*N* = 1); Congenital/Unknown (*N* = 4) | Bulbar (*N* = 7); Posterior (*N* = 7) | N/S | EPA (*N* = 11); One-stage BMGU (*N* = 2); Penile flap augmentation (*N* = 1) | Children (*N* = 5)—Mean: 10.8 years; Range: 9–13; Adolescents (*N* = 9)—Mean: 16.7 years; Range: 14–18 | No subsequent procedure required | 93% | Mean: 30 months; Range: 12–54 | Retrospective |
| Sunay et al. (18) | 2011 | 75 | Iatrogenic (*N* = 5); Traumatic (*N* = 70) | Bulbar (*N* = 38); Posterior (*N* = 37) | Mean: 2.3 cm; Range: 1.5–5.0 | EPA (*N* = 54); Pull-through urethroplasty (*N* = 20); Ureteral graft augmentation (*N* = 1) | Mean: 12.3 years; Range: 6–17 | Urinary continence, patent urethra, and absence of lower urinary tract symptoms | EPA: 69%; Pull-through urethroplasty: 70%; Ureteral graft augmentation: 100%; Overall: 69% | Mean: 43 months; Range: 12–94 | Retrospective |

*(Continued)*

**TABLE 1** | Continued

| Author | Year of study | Number of patients | Stricture etiology | Stricture location | Stricture length | Surgical approach | Age at surgery | Definition of treatment success | Success rate | Length of follow-up | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trachta et al. (19) | 2016 | 8 | Traumatic (*N* = 8) | Bulbar (*N* = 4); Posterior (*N* = 4) | N/S | EPA (*N* = 8) | Mean: 12.3 years; Range: 5–17 | No evidence of stricture in urethrography | 25% | Mean: 4.5 years; Range: 0.5–10 | Retrospective |
| Vashishtha et al. (20) | 2014 | 52 | Traumatic (*N* = 30); Inflammatory (*N* = 20); Congenital/Unknown (*N* = 2) | Bulbar and Posterior; N/S | N/S | EPA (*N* = 52) | Mean: 10.8 years; Range: 4–18 | N/S | 81% | Mean: 42.8 months; Range: 12–144 | Retrospective |
| Voelzke et al. (21) | 2012 | 26 | Traumatic (*N* = 26) | Anterior (*N* = 8); Posterior (*N* = 18) | Anterior strictures— Median: 2.5 cm; Range: 1.5–5.5; Posterior strictures— Median: 2.0 cm; Range: 1.0–5.0 | One-stage BMGU (*N* = 3); EPA (*N* = 23) | Mean: 15 years; Range: 4–18 | No evidence of stricture in urethrography, sufficient uroflowmetry, absence of lower urinary tract symptoms | Anterior strictures: 88%; Posterior strictures: 89%; Overall: 88% | Median: 0.7 years; Range: 0.07–7.8 | Retrospective |

*BMGU, buccal mucosal graft urethroplasty; EPA, excision and primary anastomosis; N/S, not specified.*

undergoing urethrotomy or dilation were grouped together and thus, outcomes were not discriminable (23, 24). Thus, the lack of granularity of data and generally small sample sizes did not allow drawing any conclusion regarding a superiority of either urethrotomy (cold knife or laser) or dilation over each other. Of note, Aboulela and colleagues compared a prospectively followed cohort of 21 children undergoing holmium laser urethrotomy to a historical cohort of 21 children undergoing cold knife urethrotomy (4). Despite there was no statistically significant difference in treatment success (i.e., no voiding difficulty with improved Qmax to $\geq$15 mL/s confirmed by a normal urethrography) between both groups ($P = 0.064$), success rates differed clinically (67 vs. 38%). However, given the small sample size and differing follow-up (median of 12 and 24 months in the holmium laser and cold knife cohort, respectively), the authors' conclusion of the superiority of laser treatment over cold knife urethrotomy should be discussed under high scrutiny.

## URETHROPLASTY

Overall, 11 studies reported on outcomes after urethroplasty (11–21) and the aforementioned four studies reported on both endoscopic treatment and open surgery (22–25) (**Tables 1**, **3**). All studies were performed retrospectively without exception. Similar to the articles on endoscopic treatments, the definitions of (surgical) treatment success were heterogeneous. In eight of the 15 studies, the authors used relatively objective criteria such as radiographic evidence of urethral patency (11, 13, 19, 21, 25) or no further need of any intervention (11, 15, 17, 24) as a surrogate for success, whereas treatment success was determined rather clinically (absence of urinary symptoms, improvement in uroflowmetry, patient satisfaction, absence of post-void residual urine) in five (12, 14, 16, 18, 23) or was not defined in two studies (20, 22). Roughly 58% of boys undergoing urethroplasty were treated by excision and primary anastomosis, followed by graft augmentation in 12%, flap urethroplasty in 9%, and pull-through urethroplasty in 6%. The reconstructive technique was not specified in 15% of patients (**Figure 3**). Follow-up intervals varied across the studies, ranging from a median follow-up of 0.7 years (21) to an average of roughly 6.8 years (24). After stratifying patients according to urethroplasty technique, average cumulative success rates were 82% (range: 25–100) for excision and primary anastomosis in 206 boys, 94% (range: 75–100) for graft augmentation in 40 boys, 97% (range: 87–100) for flap urethroplasty in 30 boys, 70% for pull-through urethroplasty in 20 boys (one study), and 77% in 51 boys in whom urethroplasty technique was not further specified (**Figure 3**). The overall cumulative success rate of urethroplasty in 347 patients (one was lost to follow-up) was 84% (range: 25–100), irrespective of the reconstructive technique used (**Tables 1**, **3**, **Figure 3**).

Given that nine of the 15 studies evaluating the role of urethroplasty in children with urethral stricture included both posterior and anterior strictures (14–22), the reporting of outcomes for isolated anterior strictures was hardly possible. Several other pitfalls have to be considered when interpreting the present data and drawing therapeutical conclusions. Overall,

**TABLE 2 |** Summary characteristics of included studies of patients who underwent endoscopic treatment (dilation or urethrotomy) for pediatric urethral stricture.

| Author | Year of study | Number of patients | Stricture etiology | Stricture location | Stricture length | Surgical approach | Age at surgery | Definition of treatment success | Success rate | Length of follow-up | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aboulela et al. (4) | 2018 | 42 | Congenital/Unknown ($N = 23$); Traumatic ($N = 10$); Iatrogenic ($N = 9$) | Bulbar/Penile ($N = 20$); Posterior ($N = 22$) | Mean: 1.0 ± 0.4 cm | Ho:YAG laser ($N = 21$; prospective cohort); Cold knife ($N = 21$; retrospective cohort) | Mean: 6.3 ± 3.2 years | No voiding difficulty with improved Qmax to ≥15 mL/s that was confirmed by a normal VCUG | Ho:YAG: 67%; Cold knife: 38%; No difference in treatment success ($P = 0.064$) | Ho:YAG: Median 12 months; Range: 6–34; Cold knife: Median 24 months; Range: 8–32; No difference in follow-up ($P = 0.1$) | Combined retrospective and prospective |
| Chiang et al. (5) | 2007 | 52 | Iatrogenic ($N = 44$); Congenital/Unknown ($N = 4$); Traumatic ($N = 2$); Postinfectious ($N = 2$) | Anterior ($N = 32$); Posterior ($N = 20$) | N/S | Guide wire and sheath dilator ($N = 52$) | Mean: 5.6 ± 2.3 years; Range: 2–18 | No clinical symptoms or no endoscopic evidence of recurrence | 39% | Mean: 4.5 ± 2.4 years; Range: 3.8–6.5 | Retrospective |
| Faerber et al. (6) | 1994 | 12 | Iatrogenic ($N = 10$); Traumatic ($N = 2$) | Anterior ($N = 12$) | <5 mm ($N = 12$) | Nd:YAG laser ($N = 12$) | Median: 7.5 years; Range: 2–18 | N/S | 75% | Median: 11.5 months; Range: 7–16 | N/S |
| Hafez et al. (7) | 2005 | 31 | Iatrogenic ($N = 25$); Congenital/Unknown ($N = 1$); Traumatic ($N = 5$) | Bulbar ($N = 15$); Penile ($N = 12$); Posterior ($N = 4$) | <1 cm ($N = 15$); ≥1 cm ($N = 16$) | Cold knife ($N = 29$); Ho:YAG laser ($N = 2$) | Mean: 11 years; Range: 2–18 | Asymptomatic voiding without clinical evidence of residual stricture (good flow rate and absence of residual urine) | 36% | Mean: 6.6 years; Range: 2–20 | Retrospective |
| Hsiao et al. (8) | 2003 | 50 | Iatrogenic ($N = 34$), Congenital/Unknown ($N = 11$), Traumatic ($N = 5$) | Bulbar ($N = 31$); Penile ($N = 12$); Posterior ($N = 6$); Unknown ($N = 1$) | N/S | Cold knife ($N = 45$); Electrocautery loop ($N = 4$); Ho:YAG laser ($N = 1$) | Mean: 7.7 years; Range: 6–17 | No symptoms for >12 months and no subsequent procedure required | 50% | Median: 2 years; Range: 1–7 ($N = 40$) | Retrospective |
| Launonen et al. (9) | 2014 | 34 | Iatrogenic ($N = 23$); Traumatic ($N = 3$); Congenital/Unknown ($N = 8$) | Bulbar ($N = 25$); Penile ($N = 7$); Bulbopenile ($N = 2$) | >2 cm ($N = 5$); ≤2 cm ($N = 29$) | Cold knife ($N = 34$) | Median: 6.3 years; Range: 0.2–16.3 | No subsequent procedure required | 26% | Median: 6.6 years; Range: 0.6–17.4 | Retrospective |
| Shoukry et al. (10) | 2016 | 29 | Iatrogenic ($N = 9$); Traumatic ($N = 6$); Congenital/Unknown ($N = 14$) | Bulbar ($N = 12$); Penile ($N = 3$); Posterior ($N = 14$) | 0.5–0.9 cm ($N = 16$); 1–2 cm ($N = 13$) | Ho:YAG laser ($N = 29$) | Median: 5.0 years; Range: 2–13 | No postoperative voiding difficulty, postoperative maximum flow rate (Qmax) >15 mL/s and normal urethrography | 62% | Range: 12–15 months | Prospective |

*Ho:YAG, holmium yttrium aluminium garnet; N/S, not specified; VCUG, voiding cystourethrography.*

**TABLE 3 |** Summary characteristics of included studies on comparative outcomes after both endoscopic and open surgical treatment for pediatric urethral stricture.

| Author | Year of study | Number of patients | Stricture etiology | Stricture location | Stricture length | Surgical approach | Age at surgery | Definition of treatment success | Success rate | Length of follow-up | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gobbi et al. (25) | 2017 | 7 | Congenital/ Unknown (*N* = 7) | Bulbar (*N* = 3); Penile (*N* = 4) | >1 cm (*N* = 4); <1cm (*N* = 3) | Urethrotomy (*N* = 2); Urethroplasty (*N* = 2); Dilation (*N* = 3) | Mean: 3.7 months ± 3.5; Range: 1–10 | Absence of urinary symptoms at follow-up, radiologic or endoscopic documentation of resolution of the stricture | Urethrotomy: 50%; Urethroplasty: 100%; Dilation: 67% | >12 months; not further specified | Retrospective |
| Banks et al. (22) | 2009 | 12 | Congenital/ Unknown (*N* = 12) | Bulbar (*N* = 10); Posterior (*N* = 2) | N/S | Urethrotomy: Cold knife (*N* = 8); Dilation (*N* = 3); Urethroplasty: EPA (*N* = 1) | <1 year (*N* = 6); Median: 14 years; Range: 3–15 (*N* = 6) | N/S | Urethrotomy: 38%; Dilation: 33%; Urethroplasty: 100% | Mean: 19 months; Range: 3–84 | Retrospective |
| Duel et al. (23) | 1998 | 38 | Iatrogenic (*N* = 38) | N/S | N/S | Urethrotomy/ Dilation (*N* = 29); Urethroplasty [Duplay tube (*N* = 3); Pedicled onlay flap (*N* = 4); Bladder mucosa tube (*N* = 1)]; Lost to follow-up (*N* = 1) | Mean at initial hypospadias repair: 2 years; Range: 0.6–5.8; Mean interval from hypospadias repair to stricture: 27 months; Range 1–150 | Absence of urinary symptoms | Urethrotomy/ Dilation: 21%; Urethroplasty: 88% | Mean: 6.3 years; Range: 0.1–13 | Retrospective |
| Gargollo et al. (24) | 2011 | 88 | Iatrogenic (*N* = 88) | Distal (*N* = 46); Mid-shaft (*N* = 11); Proximal (*N* = 31) | Mean: 1.7 ± 0.7 cm (*N* = 37) | Dilation/ Urethrotomy (*N* = 39); Urethroplasty: technique N/S (*N* = 49) | Dilation/ Urethrotomy— Mean: 64.6 ± 47.5 months; Urethroplasty— Mean: 57.1 ± 49.1 months | Absence of symptoms for >12 months and no subsequent procedure required | Dilation/ Urethrotomy: 38%; Urethroplasty: 53%; Overall: 47% | Dilation/ Urethrotomy— Mean: 73.8 ± 49.9 months; Urethroplasty— Mean: 81.0 ± 63.1 months | Retrospective |

*EPA, excision and primary anastomosis; N/S, not specified.*

the evidence on which this review was based on was very low with almost all studies being invariably of retrospective nature. In addition, the reported outcomes in the studies included into this review lack homogeneity, as the definition of treatment success was chosen at the discretion of each author—an issue which is seen quite often in reconstructive urology and it is still an ongoing debate on how to define success after reconstructive urological surgery (27, 28). Furthermore, a detailed assessment of graft placement techniques such as ventral, dorsal or lateral placement and differences in outcomes was not possible given the lack of granularity within the primary data.

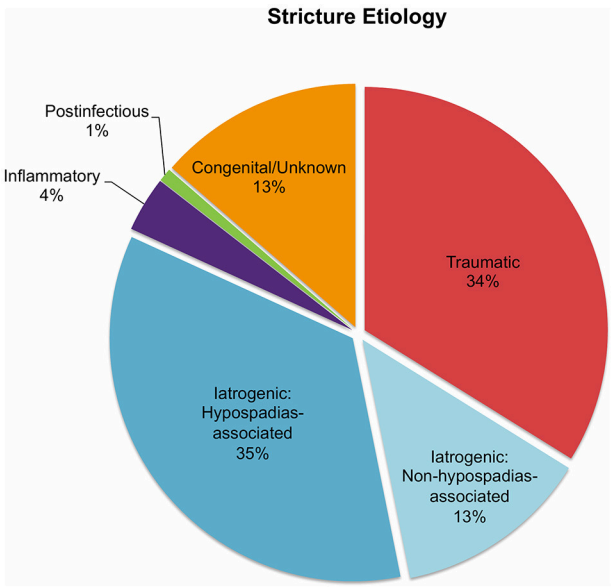


**FIGURE 1 |** Pie charts reporting the proportions of urethral stricture etiology in all 682 patients included into the present literature review.

Generally, several stricture characteristics have to be considered when opting for a reconstructive technique. Length, location, etiology, and previous interventions may hereby guide in treatment decisions. The majority of the children were treated by excision and primary anastomosis, a feasible option in short posterior or bulbar strictures <1 cm. Considering the studies included into this review, success rates after graft augmentation or flap urethroplasty were markedly higher compared to those in patients who underwent excision and primary anastomosis (roughly 95 vs. 82%, respectively; **Figure 3**). The aforementioned limitations of the present data left aside, one should always keep in mind the anatomical differences in children as opposed to adults when favoring one technique over another. The urethral caliber is smaller, the tissue more delicate and less elastic, and many children have a history of multiple surgical interventions, specifically in case of iatrogenic hypospadias-associated urethral strictures. Hypospadias repair is the leading cause of subsequent urethral stricture formation and this is somehow reflected by roughly 50% of the strictures in patients included into this review were caused iatrogenically. Of note, roughly three-fourths of these patients had a history of previous hypospadias surgery (**Figure 1**). Given that pronounced scar formation and lack of sufficient sponge tissue hamper an adequate reconstruction significantly, some authors have suggested additive maneuvers to improve vascular supply and tissue coverage. Scarred tissue is commonly attached firmly to the cavernous bodies, which complicates urethral mobilization. On the other hand, ventral placement of the graft lacks the support of the corporeal bodies, which may promote formation of diverticula and sacculation. Djordjevic et al. introduced a combined technique of a ventral

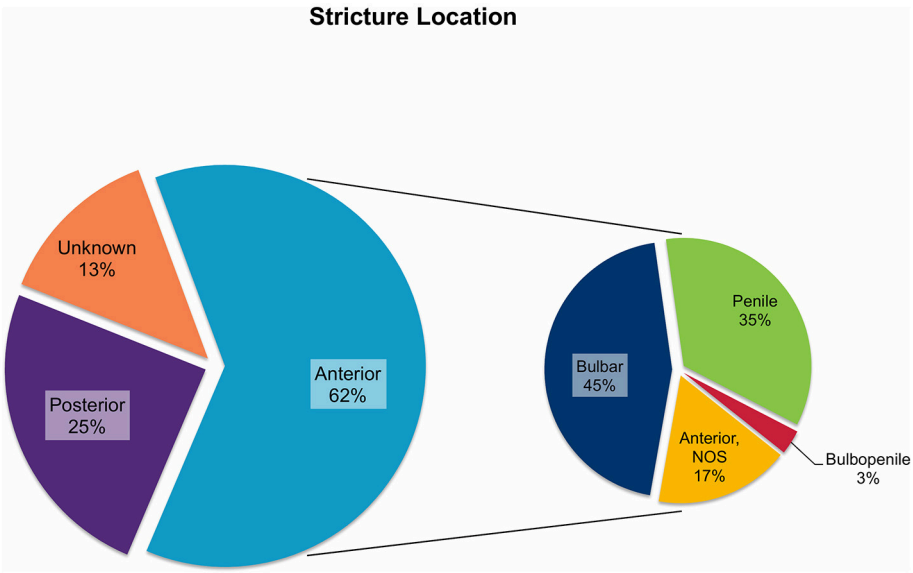


**FIGURE 2 |** Pie charts reporting the proportions of urethral stricture location in all 682 patients included into the present literature review. NOS, not otherwise specified.

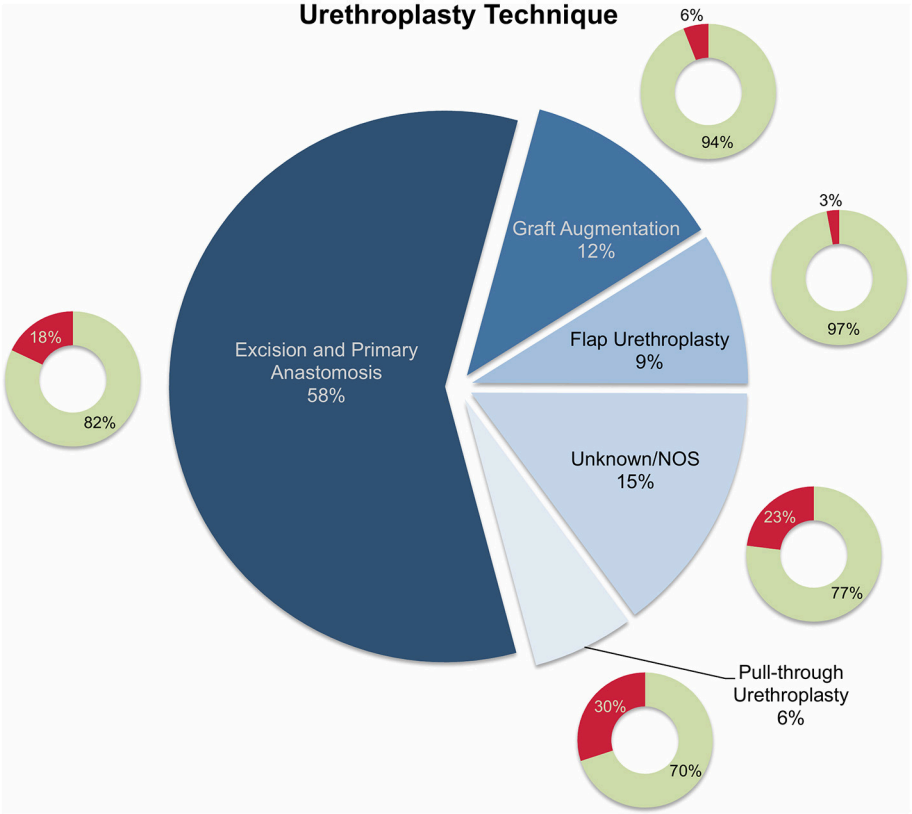


**FIGURE 3 |** Pie chart reporting the proportions of different reconstructive techniques used in 347 patients who underwent urethroplasty and were included into the present literature review. The smaller doughnut charts represent the treatment success rates for each technique (green: success; red: failure). NOS, not otherwise specified.

only buccal mucosal graft with an anchoring of the graft to the surrounding periurethral tissue to prevent folding and retraction. In 15 boys with urethral stricture following failed hypospadias surgery, the success rate was 100% after a mean follow-up of 37 months, and only one boy underwent a minor fistula repair (13).

Impressive data with regard to comparative outcomes in stricture treatment following hypospadias repair have been presented by Duel et al. (23) The authors compared eight children who underwent upfront urethroplasty to 29 children who underwent urethrotomy and found that those undergoing open surgery fared significantly better (88 vs. 21% success at a mean follow-up of 6.3 years). Similar but somehow less pronounced findings were made by Gargollo et al. (24) who also demonstrated a clinically relevant superiority of initial urethroplasty over endoscopic treatment (53 vs. 38% success at a follow-up of roughly 6 years; $P > 0.05$) in patients with iatrogenic stricture after hypospadias repair. Interestingly, the authors evaluated secondary success rates after another procedure in case of stricture recurrence and found that success rates ranged between roughly 60–70% whenever urethroplasty was performed at any time during follow-up, whereas repeat urethrotomy was successful in only 17% of patients (24). Whereas, the case series by Gobbi et al. (25) and Banks et al. (22) take the same line for congenital strictures, patient samples are too small to draw reliable conclusions.

A clear distinction between inflammatory and postinfectious strictures in children is commonly not feasible. There is some evidence suggesting an inflammatory etiology of stricture formation caused by lichen sclerosus (29), several autoimmune disorders (26), bulbar urethritis, and urethrorrhagia (30). Postinfectious strictures are mainly caused by recurrent gonococcal urethritis (26). Inflammatory strictures caused by lichen sclerosus are rare in children (**Figure 1**), but nevertheless pose a significant challenge to the reconstructive surgeon. Generally, repeat procedures such as multiple urethrotomies should be avoided and the lichenoid tissue should be dissected in order to avoid excessive scar formation and mitigate the need of further treatment. Currently, the use of genital skin as a tissue flap is not considered appropriate, given that it remains prone to the same disease process (31). Thus, promising outcomes using non-skin, oral mucosal grafts have been reported in the adult literature (32, 33), and Ashraf et al. recently reported on five boys who underwent one-stage Asopa buccal mucosal graft urethroplasty for lichen sclerosus-associated penile urethral stricture with a median length of 2.7 cm. There was no treatment failure at a median follow-up of roughly 3 years (12).

## CONCLUSIONS

Although there are several surgical options at hand for pediatric urethral stricture, the paucity of literature, which is mainly based on small monocentric series, often hampers treatment decisions for this rare disease, specifically when opting for therapeutical sequences, and gauging different strategies. However, there is some evidence available and when meticulously summarizing individual patient level data, the therapeutical perspective may be broadened, even if high-level evidence from multi-institutional, prospective collaborations with sound statistical methods are currently lacking. Pediatric anterior urethral strictures are mostly iatrogenically caused of which the majority of cases are hypospadias-associated, followed by traumatic, and congenital strictures. Endoscopic strategies such as dilation and direct vision internal cold knife or laser urethrotomy are ineffective in the long-term and should not be chosen as a first-line treatment. Urethroplasty should be preferred as definitive therapy to avoid multiple interventions and diminish clinical visits and a long time of suffering. Excision and primary anastomosis may be preferred if the stricture is short and mobilization is anatomically feasible with reported cumulative success rates of roughly 82%. Graft augmentation or flap urethroplasty did perform somewhat better, with a cumulative success rate of roughly 95% when performed in referral centers in capable hands. However, sample sizes are small and thus, results should be interpreted with caution and no unequivocal recommendation can be made to favor one open surgical approach over the other. More importantly, one highly relevant outcome measure is commonly missing in the literature, as there is virtually no data on functional outcomes such as erectile and sexual function, urinary continence, and body image or cosmetic results following surgery for pediatric urethral stricture. This comes along with short follow-up periods and inconsistency and heterogeneity in outcome definitions. Thus, researchers are challenged to establish retrospective and prospective multi-institutional collaborations, incorporating granular patient level data with adequately defined outcome measures to advance our knowledge in this relatively unattended field of reconstructive urology.

## AUTHOR CONTRIBUTIONS

MV: primary responsibility for communication with the journal during the manuscript submission, literature review, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work. LW: literature review, critical revision of the article, final approval of the version to be published, agreement to be accountable for all aspects of the work. SR: critical revision of the article, final approval of the version to be published, agreement to be accountable for all aspects of the work. MF: supervision, critical revision of the article, final approval of the version to be published, agreement to be accountable for all aspects of the work.

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REVIEW
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# Traumatic Posterior Urethral Strictures in Children and Adolescents

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**Background:** Management of partial or complete traumatic urethral disruptions of the posterior urethra in children and adolescents, secondary to pelvic fracture poses a challenge. Controversy exists as to the correct acute treatment of posterior urethral injuries and delayed management of PFPUDDs. We reviewed the urological literature related to the treatment of traumatic posterior urethral injuries and delayed repair of these distraction defects in children and adolescents.

**Material and Methods:** There are few long-term outcomes studies of patients who underwent PFPUDDs repairs in childhood; most reports included few cases with short follow up. We excluded studies in which the cohort of patients was heterogeneous in terms of stricture disease, etiology and location.

**Results:** Primary cystostomy and delayed urethroplasty is the traditional management for PFPUIs. Immediate repair is rarely possible to perform. Realignment of posterior urethral rupture in children is indicated in special situations: (a) concomitant bladder neck tears, (b) associated rectal lacerations, (c) long disruptions of the urethral ends. Before delayed reconstruction ascending urethrography and micturating cystourethrogram along with retrograde and antegrade urethroscopy define site and length of the urethral gap. However, the most accurate evaluation of the characteristics of the distraction defect is made when surgical exposure reveals the complexity of the ruptured urethra. Partial ruptures may be managed with urethral stenting or suprapubic cystostomy, which may result in a patent urethra or a short stricture treated by optical urethrotomy. The gold standard treatment for PFPUDDs in children is deferred excision of pelvic fibrosis and bulbo-prostatic tension-free anastomosis, provided a healthy anterior urethra is present. Timing of delayed repair is at 3 to 4 months after trauma. Some urologists prefer either the perineal access or the transpubic approach to restore urethral continuity in children with PFPUDDs. Substitution urethroplasties are used in children with PFPUDDs, when anastomotic repair can't be achieved due to severe damage of the bulbar urethra.

**Conclusion:** As evidenced in this review the progressive perineo-abdominal partial transpubic anastomotic repair has advantages over the isolated perineal anastomotic approach in patients with "complex" PFPUDD. This approach provides wider exposure and facilitates reconstruction of long or complicated posterior urethral distraction defects

**Keywords: urethra, injuries, urethral stricture, surgery, children, adolescents**

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## INTRODUCTION

Trauma is a major cause of morbidity and mortality in children (1). Urethral trauma producing stricture disease in pediatric patients most often results from fracture of the pelvis, straddle injuries or iatrogenic urethral manipulation (2). The incidence of pediatric PFUIs has been estimated to be between 1 and 5%; however, Tarman et al. reported in a series of 212 children with fracture of the pelvis that the occurrence of urethral lesions was <1% (3, 4). In childhood, the majority of PFPUIs occur as pedestrians hit by a motor vehicle rather than as passengers of a vehicle involved in an accident (5–7).

A distinction should be made between the terms urethral stricture and rupture of the urethra. The former is a narrowing of the urethral canal as a result of changes in its walls caused either by inflammation or by trauma, while the latter results in partial or complete separation of the injured urethral extremities, followed by the development of dense fibrous tissue between the torn urethral ends (8). Posterior urethral strictures are generally the consequence of endoscopic trauma at the site of the sphincter active membranous urethra, but urethral continuity is preserved. In adults, PFPUIs usually involve the membranous urethra at some point between the apex of the prostate and the posterior bulbar urethra, and commonly result in a short urethral distraction defect associated with localized pelvic fibrosis (9, 10). Turner Warwick introduced the term "complex" posterior urethral distraction defect due to a pelvic fracture (PFPUDD) when one or more of the following features are present: (a) the distraction defect length is long (≥3 cm) surrounded by extensive pelvic fibrosis and (b) it is accompanied by para-urethral diverticula, false passages, fistulas, rectal tears or simultaneous bladder neck lesion. These complex urethral distraction defects require a wider surgical exposure to restore urethral continuity and to correct associated adjacent traumatized structures (8).

Although PFPUDD pathogenesis in children tends to follow a similar pattern to the one in adults, several key elements require consideration. Some authors have inferred that the location of the traumatic urethral injury in children is less predictable due to the abdominal position of the bladder and immaturity of the prostate (11). Further factors to consider in pediatric patients include: (a) urethral distraction defects tend to be longer than in adults because of marked upwards displacement of the bladder and prostate, (b) double injuries at the bladder neck and the membranous urethra are more frequently observed and (c) pre-pubertal perineum size may make it difficult to reach a high lying proximal urethral end (12–14).

We reviewed previous manuscripts by searching PubMed Medline electronic database for clinically relevant articles. There are not many long-term outcomes studies of patients who underwent PFPUDDs repairs in childhood; most published reports have included few cases with short follow-up. We excluded studies in which the pediatric patients were heterogeneous in terms of stricture disease etiology and location. Thus, the objective of this review will focus on the urological literature related to the acute management of traumatic injuries of the posterior urethra and delayed repair of posttraumatic obliterate posterior distraction defects in children and adolescents.

**Abbreviations:** PFPUIs, pelvic fracture posterior urethral injuries; PFPUDDs, pelvic fracture posterior urethral distraction defects.

## MATERIALS AND METHODS

Patients who suffer from severe pelvic injury are usually in shock and urinary symptoms are often overlooked. At that moment, clinical differentiation between an extra-peritoneal bladder lesion and a posterior urethral rupture is difficult; however, if a distended bladder is palpated, the rupture might be urethral. Upon suspicion of urethral injury in any boy who has had a pelvic fracture, appropriate evaluation is mandatory when the clinical condition of the patient is stable. Urethral catheterization is to be avoided in order not to aggravate the urethral injury or introduce infection to the pelvic hematoma (6, 8). Retrograde urethrography in the oblique position is the most effective examination to diagnose a urethral lesion (7, 8, 13). Water—soluble contrast medium in a concentration of 20 to 30% may be used for retrograde urethrogram. This study is terminated as soon as extravasation of contrast material, with or without total loss of urethral continuity, is visualized; excessive pressure during the injection of contrast medium into the urethra may cause urethra-venous or urethra-cavernous backflow. Extravasation of contrast medium is a sign of partial or circumferential rupture. If fluoroscopy equipment is not available, this examination can be done with a portable apparatus in the emergency room (7, 8). When computed tomography equipment (CT scan) can be used, it is helpful to investigate the genitourinary tract and provides valuable information. CT scan permits excluding major injuries in the abdomen, diagnosing types of pelvic fracture and recognizing the position of the bladder after the acute trauma. A high—riding bladder is an indirect radiographic sign of posterior urethral injury, though sometimes the urethra is only stretched without rupture of its wall.

Cystographic appearance of the bladder base gives valuable information; a closed bladder neck may be indirect evidence of integrity of the proximal sphincter mechanism. Likewise, an open and funneled bladder neck should not be mistaken for associated vesical neck lesion (15). In contrast, a cystogram showing a distorted bladder neck and extravasation of contrast medium raises the suspicion of a damaged proximal sphincter (8, 13). Some authors continue to relate incontinence, severity of urethral pelvis trauma and associated bladder neck injury at the time of trauma. The importance of preserving the bladder neck sphincter function in these cases is mandatory to maintain continence after urethroplasty, as the distal sphincter mechanism at the membranous urethra is damaged at the original trauma (8, 13, 15, 16).

Traditional teaching suggests that the posterior urethra is torn off at the apex of the prostate above the urogenital diaphragm (17). However, cadaveric studies have reviewed the urogenital diaphragm anatomy and documented the non-existence of a superior layer in this diaphragm, now named perineal membrane (18). These authors encountered that the muscles surrounding

the membranous urethra are connected with the muscles of the prostatic urethra, and with the perineal fascia, but not to the bulbar urethra (18). Thus, contrary to the classic anatomy description, the terminal portion of the membranous urethra, before entering the bulbar channel, is the weakest point at which the posterior urethra is exposed to traumatic rupture (19). If the rupture occurs at the distal portion of the membranous urethra, the posterior bulbar channel may be also involved (19, 20). Thus, when a violent external force causes a pelvic fracture, the pelvis is compressed and the bladder and prostate are moved upwards, stretching the membranous urethra, firmly fixed to the perineal fascia. If the trauma force exceeds the elasticity of the membranous urethra, a partial or complete rupture will take place at the membranous-bulbar urethral junction (6, 21). In cases of circumferential rupture, if the distal end of the membranous urethra remains attached to the perineal fascia the separation is less marked. Yet, if the trauma disrupts the perineal membrane the distal urethral end will be displaced to the perineum, with marked separation of the urethral extremities (21).

Colapinto and McCallum provided a classification of posterior urethral injuries: type I, posterior urethra elongated but intact; type II, partial or complete lesion of the membranous urethra above the perineal fascia and type III, partial or complete urethral tear at the bulbar-membranous junction with disruption of the urogenital diaphragm (21). In type III urethral lesion extravasation of contrast medium begins in the perineum and extends to the pelvis. In children, type III injuries seem to occur more frequently than the classic type II lesion (22). Very few authors reported pelvic fracture disruption across the prostate gland (11, 23). Boone et al. pointed out 3 distinct sites of PFPUIs in pediatric patients: suprapubic, transprostatic and prostate-membranous, while Al Rifael et al. reported ruptures across the prostate in only 3 childrens (11, 23). In the writer's experience as well as in the reports of other authors, the site of PFPUDD in children is invariably sub-prostatic (7, 12, 13). On occasions, the inframontanal prostatic urethra was also involved. These findings were confirmed by visualization of the verumontanum at the distal end of the proximal urethral extremity on preoperative antegrade urethroscopy and in the course of surgical repair (12, 13, 22). Interestingly, when concomitant bladder neck injuries were present they were longitudinal tears rather than complete transverse cuts.

Before deferred repair, pediatric patients need to be re-evaluated to define the site and length of the urethral defect, bladder neck morphology, and anatomic delineation of the anterior urethra and whether local complications such as fistulas, pseudo diverticula, or stones are present (12, 13, 15). Radiographic evaluation begins with plain radiograph of the pelvis. Combined antegrade cystography and retrograde urethrogram, as well as urethroscopy and cystourethroscopy through the suprapubic tract under anesthesia define the anatomical features of the distraction defect. We cannot overemphasize the importance of filling the prostatic urethra during cystography while retrograde urethrography is done simultaneously, to accurately delineate the length of the distraction defect (13). This difficulty is overcome with patience by repeating the cystography with different volumes of contrast medium. When the proximal urethra is not filled with contrast medium, the length of the distraction defect cannot be properly assessed.

Morey and McAninch advocated that magnetic resonance imaging (MRI) may be considered a better option to define the length and location of the urethral defect (24). Koraitim also affirmed that MRI is helpful in evaluating the anatomical features of the urethral gap and severity of prostatic displacement in 86 and 89% of 21 patients with PFPUDD, respectively (25). Limitations of MRI studies in children are that, a full bladder and a distended anterior urethra are needed with the child in a claustrophobic scenario (26).

## RESULTS

Several questions arise in determining the management of acute traumatic posterior urethral injuries as well as in the treatment of delayed posttraumatic posterior urethral distraction defects. It is agreed that in the presence of shock, intense hemorrhage and severe associated injuries, well-judged treatment should be initially directed to stabilize the patient and treat serious simultaneous lesions, while management of the urethral lesion should be deferred. Pelvic fractures have been treated for years by conventional methods with pelvic slings or spica casts; however, nowadays, external fixation is the treatment of choice, in the presence of unstable ring fractures (27).

Early surgical exploration and suture repair have been proposed in the past, but are difficult to accomplish due to the grave condition of the patient and the limited experience of urologists managing these severe urethral injuries (17). Realignment of complete rupture of the posterior urethra in adult patients corrects lateral urethral displacement at the disrupted site, reduces the length of the distraction defect and simplifies subsequent delayed urethral repair (28). Techniques to realign the traumatized urethra differ somewhat among them; procedures can be performed either blindly or endoscopically. Endoscopic realignment is a more advantageous method, enables the urologist to identify incomplete urethral tears, which can be rapidly stented. However, in adults and particularly in children long-term reported results with this line of treatment are poor and the majority of patients require additional procedures to achieve a less than satisfactory outcome (26, 29, 30). It is agreed that in spite of these limitations, early endoscopic realignment should be reserved for pediatric patients in the following situations: (a) when urethral distraction defect is extensive, (b) when concomitant bladder neck tear is present, and (c) when associated rectal laceration requires suture (7, 13).

Nowadays, with continued refinement in surgical techniques that can treat posttraumatic urethral distraction defects with good postoperative results, low incidence of impotence and incontinence, most of the urologists prefer to place a suprapubic cystostomy followed by deferred urethral reconstruction (7, 12, 13, 23). Partial urethral disruptions may or may not result in a continuity stricture, with minimal damage of the intrinsic element of the distal sphincter mechanism. Partial tears of the

urethra are managed by suprapubic cystostomy followed by successive retrograde urethrograms or urinary flow rates which will show the evolution of the lesion. If extravasation of contrast medium ceases, a micturition cystogram is performed before removing the cystostomy tube. If a stricture develops, it may respond to urethral dilatation or direct optical urethrotomy (8).

On the other hand, circumferential ruptures will almost always harm the distal sphincter mechanism and lead to a relatively short urethral distraction defect with reduced pelvic fibrosis (9, 10). Less frequently, complete ruptures may develop a long urethral distraction defect with extensive fibrous tissue in between the separated urethral ends with or without complex associated local traumatized structures (8). Suprapubic cystotomy provides effective urinary drainage without disturbing the pelvic hematoma and avoids the risk of major blood loss in a critically ill child. The main drawback is the long period during which the patient has a cystostomy before definitive surgical repair.

## DISCUSSION

Debate is still present between those urologists who favor early urethral realignment with or without primary reconstruction of the transected urethra vs. those who advocate primary suprapubic diversion of urine and deferred repair of the urethra (17, 31). The past surgical treatment was sustained on the basis that the overcoming obliterate urethral distraction defect was not possible to treat with the surgical techniques then available. Alternatively, other authors have proposed retropubic exploration 7 to 10 days after initial trauma, when the pelvic hematoma has attained a more organized condition and the torn urethral ends can be better assessed to perform an end to end anastomosis over an indwelling catheter (8, 32). However, secondary strictures or persistent urethral distraction defects, incontinence, and erectile dysfunction were frequently found with this line of treatment (32). Moreover, in a report where primary suturing was performed, 4 of the 6 children treated in this way developed a stricture at the site of the primary anastomotic urethroplasty (15). Nerli et al. reported that 50% of their pediatric patients undergoing primary realignment needed additional endoscopic urethrotomies, while 3 of the cases required urethroplasty to manage a resultant stricture (33). Similar findings was reported in adults by Leddy et al. (34) Furthermore, in another retrospective study, no significant difference was found in the length of the established urethral gap in boys with complete PFPUI treated with early urethral realignment or suprapubic cystostomy (15). These findings are in consonance with Radge and McInnes observations during transpubic exploration of proximal urethral ruptures; these authorities found that even catheter traction did not approximate the stented ruptured urethral extremities (35).

The aim of deferred urethral reconstruction for children with PFPUDD is to restore urethral continuity with an adequate caliber and minimal life-long complications, as recurrent strictures, incontinence or erectile dysfunction. A variety of surgical procedures have been proposed for the delayed repair of PFPUDDs: urethral dilatation, endoscopic techniques which include direct optical internal urethrotomy (DVIU), substitution procedures and deferred tension-free mucosa to mucosa anastomotic repair, when the bulbar urethra is normal (13, 36).

Urethral dilatation and internal urethrotomies for PFPUDD are not acceptable in children; reported results have been poor, and patients undergoing these procedures required additional surgical operations (36, 37). DVIU has been found advantageous for both the management of annular membranous strictures following partial urethral injuries or for short non-obliterative strictures after failed post-traumatic primary anastomotic repair (38). In selected cases with minimal posterior urethral distraction defects some authors advocate the use of DVIU, which may create a passage through the dense pelvic fibrosis. However, this method is usually followed by long-term urethral dilatations and ultimately requires urethroplasty repair. Furthermore, false passages into the bladder neck or fistula development between the torn urethra and the rectum can occur with this treatment modality. Consequently, this line of treatment should be avoided in the case of obliterative membranous urethral distraction defects following pelvic fracture (37, 39).

Substitution procedures for PFPUDDs are only required when there is a specific indication: (a) simultaneous injury of the anterior urethra; (b) should the patient have a concomitant anterior urethral stricture or the presence of a congenital abnormality. In these situations the anterior urethra cannot be mobilized as a flap because retrograde blood flow along the bulbo-penile spongy tissue is impaired (8, 37). A variety of substitution procedures and their modifications have demonstrated to be reliable only during short periods of time. Clearly, no urethral substitute is as good as the urethra itself. Reported failure rate of 54% after urethra-scrotal inlay is valid evidence of its poor effectiveness in the treatment of PFPUDDs (13, 37). Alternatively, some authors have described a two-stage urethroplasty option for patients with multiple urethral strictures or in cases with several failed previous urethroplasties..The principle of this technique consists in interposing a meshed split thickness skin graft between the transected urethral ends and the perineal skin margins. Once the graft has grown, the neo-urethra is constructed in a second stage with the non-hair bearing skin from a portion of the graft (40). Other authors advocate the use of foreskin or penile skin on a pedicled basis as a one-stage procedure (41). Finally, full-thickness skin grafts do poorly in PFPUDDs cases due to the lack of a well-vascularized recipient site for the graft.

At the present day, there is almost complete consensus that restoration of urethral continuity in children and adults with PFPUDDs by anastomotic bulbo-prostatic repair is the gold standard procedure, provided the anterior urethra is healthy (7, 8, 13, 42). Success in anastomotic urethroplasty is dependent on adequate surgical exposure, excision of all fibrous tissue occupying the distraction defect, mobilization of the normal bulbar urethra, fixation of healthy mucosa at the edges of the bulbar and prostatic urethral ends and performing a tension-free spatulated anastomosis, when appropriate blood supply is present through the urethra (43, 44). A variety of surgical access options are available to perform the anastomotic repair: (a)

perineal approach, (b) elaborated 1-stage perineal access, (c) transpubic (partial or total) approach, (d) progressive perineal-abdominal (transpubic) approach, and (e) posterior sagittal access (8, 42, 45, 46).

It is interesting to try to understand why some urologists prefer either the transpubic approach or the perineal access alone to restore urethral continuity in children with PFPUDDs (42, 45). One reason why these urologists make such a decision may be related to the preference of preoperative radiographic evaluation of the urethral distraction defect, rather than to the validation of the anatomical features of the traumatized urethra in the course of surgery. A priori, it could be argued that judging the characteristics of the urethral distraction defect only on the basis of preoperative imaging studies may be misleading; thus, under this scenario the perineal approach alone may result insufficient to resolve a "complex" distraction defect (8, 13, 22). Hence, the perineal access needs to be extended to achieve a wider exposure, in order to perform a tension-free spatulated anastomosis, which is extremely difficult if the patient is already placed in the high lithotomy position, frequently used in the perineal approach.

Two surgical procedures have been proposed for adult patients to solve this difficulty: the perineo-abdominal (transpubic) progression approach and the elaborated 1-stage perineal access (8, 45). The first procedure enables progression from a perineal to a perineal-abdominal access with or without partial pubectomy, according to the intra operative anatomical features of the urethral distraction defect and allowing supracrural re-routing of the mobilized urethra if needed (47). While the elaborated perineal technique provides stepwise maneuvers to accomplish a tension-free anastomosis: (a) mobilization of the bulbar urethra, (b) separation of the proximal corporeal bodies, (c) resection of the inferior margin of the subpubic arch, and (d) the possibility to reroute the anterior urethra around one corporeal body to shorten the course of the mobilized bulbar urethra (45). In a review of 38 articles with substantial contribution to the management of PFPUDDs, Hosseini et al reported a success rate of 82% to 95% with the perineal anastomotic repair (48). Singla et al. in 28 patients with PFPUDD whose mean age was 12 years at the time of injury, performed perineal anastomotic repair in 27 cases, with a success rate of 75%, but follow up ranged from 3 to 58 months (49). El-Sheikh et al also treated 15 children between 5 and 17 years of age with perineal anastomotic urethroplasty. Initial success rate was 80% with a mean follow-up of 25 months (50). Finally, Orabi et al managed 47 boys (mean age 9 years) by perineal anastomotic repair in 40, perineal anastomotic urethroplasty with inferior pubectomy in 3, transpubic repair in 4, and substitution urethroplasty in 3 other cases. Mean follow-up was 4.5 years (51). Three children who underwent perineal repair had a re-stricture, 1 after transpubic repair due to callus formation, and 1 after substitution repair (51).

It must be recognized that the progressive perineo-abdominal procedure has advantages over the elaborated perineal technique when treating pediatric patients: (a) provides a wider exposure, (b) facilitates restoration of urethral continuity in the presence of a high riding proximal urethral end and extensive fibrosis, and (c) allows concomitant repair of a damaged bladder neck and the treatment of traumatized adjacent structures. Furthermore, in the hands of the writers the elaborated perineal technique, when applied to prepubertal boys, did not allowed intercrural space development and, consequently, inferior pubectomy.

Furthermore, other authors have shown that anastomotic urethroplasty performed through perineal-abdominal transpubic access in children with PFPUDD have a success rates >90% (7, 13). Interestingly, Al- Rifaei et al. treated 20 children (2 to 18 years old) with PFPUDD. The level of the rupture was at the membranous urethra in 17 cases, across the prostate in 3 and with complete obliteration of the entire prostatic urethra in one. The approach used was perineal in 4, transpubic-abdomino- perineal anastomotic in 16. In 1 of these latter patients, a distally based anterior bladder tube was performed. Good postoperative results were noted in all perineal repairs, but 2 cases treated transpubically had recurrent strictures and 4 developed incontinence. All incontinent cases had preoperative damage of the proximal sphincter mechanism (23).

Four years later, Kardar et al treated 12 boys (3–12 years)with bulbo-prostatic anastomosis. All but one patient underwent a perineal-abdominal transpubic approach (partial pubectomy in 7 and total in 4). After mean follow-up of 22 months, there were no recurrent strictures and 8 boys were continent. Erections were noted before and after anastomotic repair in 66% of these cases (12). Likewise, Das et al reported 100% success after using transpubic urethroplasty in 10 children, all of whom are continent (52). On the basis of this line of treatment, Patil followed 5 of 30 patients 9 to13 years old, who had been treated transpubically into adulthood. All were unimpeded in daily activities, sports and sexual function (53).

Ultimately, three articles with an important number of patients and long follow-up, referred to the outcomes of the perineal and combined perineal- abdominal transpubic anastomotic repair. In the first study, Koraitim reported excellent results in 69 boys (3–15 years) with either transperineal (93%) or transpubic anastomotic repair (91%), as opposed to a failure rate of 54% with urethroscrtal inlay procedure (13). This author used the perineal approach in 42 patients when the urethral gap was up to 3 cm and transpubic repair in 23 cases with longer defects (13). In another study, risk factors that may complicate a satisfactory anastomotic urethroplasty outcome were analyzed, comparing 15 boys with PFPUDD treated with perineal bulbo-prostatic anastomosis vs. a similar number of cases managed with the perineal-abdominal transpubic anastomosis repair (22). Median follow-up of these cases was 8.5 years. Stricture-free rate in patients managed only through the perineum was 84 vs. 100% in those treated with combined (transpubic) access. Retrospectively, failed perineal urethroplasty was attributed to improper patient selection as all cases had distraction defects of at least 3 cm of length with significant cephalic displacement of the prostate. These 4 failed patients were stricture free after a combined perineal- abdominal (transpubic) anastomotic repair (3) and optical urethrotomy (1). Incontinence developed in 1 boy in the perineal group, and in 3 in the combined (tranpubic) approach, attributed to the violence of initial trauma and concomitant bladder neck tears. This study highlighted that in children with PFPUDD, surgical repair should begin through a perineum exposure and when tension–free anastomosis was not

possible to perform through this access an abdominal (partial pubectomy) approach is required for the resolution of the distraction defect (22).

A more recent study reviewed 49 male children and adolescents aged 3.5 to 17.5 years (median 9.5) with PFPUDDs who underwent delayed bulbo-prostatic anastomosis. Median urethral gap defect was 3 cm (range 2–6). Access was perineal in 28 and perineal/partial pubectomy in 29. Median follow-up was 6.5 years (range 5–22) (7). Five perineal anastomotic repair cases developed recurrent strictures at the anastomosis site, successfully managed with additional perineal/partial pubectomy anastomosis (4) and internal urethrotomy (1). Primary and overall success rate was 89, 7 and 100%, respectively. Urinary incontinence occurred in 9 cases: 2 had overflow incontinence and performed self- catheterization,1 developed sphincter incontinence and required AUS placement, while 4 of 6 cases with mild stress incontinence achieved dryness at pubertal age. Retrospectively, associated bladder neck lesions at trauma time were noted in 5 of these patients. Three patients with erectile dysfunction before urethral reconstruction remained with erectile dysfunction (7).

Finally, a 9 year old patient with a PFPUDD was treated with anastomotic urethroplasty via an anterior sagittal approach without splitting the rectum with a good post-operative result though follow-up was only 18 months (54). The author reported "an excellent exposure of the posterior urethra."

Postoperative follow-up involved clinical visits and retrograde urethrogram 1 month after repair, repeated at 1, 5, 10, and 15 years thereafter. Uroflowmetry was indicated yearly. Patients with incontinence after urethroplasty underwent video-urodynamic studies. Erectile dysfunction was identified in older children when they were able to inform of this disability (7).

It is noteworthy to admit limitations of this review. The retrospective nature of this study has the inherent flaws associated with this review design. Moreover, the exact mechanism of erectile dysfunction was not investigated in the manuscript reviewed, in the kind of detail required because of patients' age.

## CONCLUSIONS

In children, urethral injury, though uncommon, is an important cause of morbidity. Initial treatment of posttraumatic posterior urethral injuries caused by pelvic fractures should be directed to stabilize the patient and treat life-threatening associated injuries. The following step is to diagnose the urethral lesion by retrograde urethrography; if present, suprapubic urine drainage should be performed in the majority cases. Immediate realignment procedures are only required in children with PFPUI associated with concomitant bladder neck tear, simultaneous rectal laceration or when urethral distraction defect is extensive. Timing for deferred repair is postponed until local healing is complete and the hematoma has contracted, generally 3–4 months after original trauma. Preoperative assessment of the established urethral distraction defect includes combined radiographic studies and urethroscopy findings in order to define the anatomical features of the urethral distracting defect. However, precise delineation of the PFPUDD is more accurately determined at the time of surgical reconstruction. As evidenced in this review, when a healthy anterior urethra is present, resection of the pelvic fibrosis and end to end spatulated anastomosis is the gold standard technique to treat PFPUDDs. The procedure should be initiated through the perineum, only to be extended to lower abdomen, with or without a partial transpubic access, when long distraction defects and complex associations, such as simultaneous bladder neck lesions, recto-urethral fistulas or periurethral cavities are present. Substitution urethroplasty for PFPUDD are rarely necessary, reserved for cases with associated anterior urethral strictures, congenital abnormalities or in cases with several failed previous urethroplasties.

## ETHICS STATEMENT

Approval was granted by the hospital review board.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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# Tissue Engineering in Pediatric Bladder Reconstruction—The Road to Success

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Several congenital disorders can cause end stage bladder disease and possibly renal damage in children. The current gold standard therapy is enterocystoplasty, a bladder augmentation using an intestinal segment. However, the use of bowel tissue is associated with numerous complications such as metabolic disturbance, stone formation, urine leakage, chronic infections, and malignancy. Urinary diversions using engineered bladder tissue would obviate the need for bowel for bladder reconstruction. Despite impressive progress in the field of bladder tissue engineering over the past decades, the successful transfer of the approach into clinical routine still represents a major challenge. In this review, we discuss major achievements and challenges in bladder tissue regeneration with a focus on different strategies to overcome the obstacles and to meet the need for living functional tissue replacements with a good growth potential and a long life span matching the pediatric population.

**Keywords: myelomeningocele, neurogenic bladder, bladder augmentation, tissue engineering, stem cells, pediatric**

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## INTRODUCTION

Congenital disorders such as posterior urethral valves, bladder extrophy, and neurogenic bladder result in reduced bladder capacity, impaired compliance, incontinence, and possibly renal damage. Despite decades of experience in the management of end stage bladder disease, current therapy options are not curative. Enterocystoplasty—bladder augmentation using an intestinal segment—is the gold standard therapy if medical management fails. However, it is associated with severe complications, including metabolic disturbances, stone formation, urine leakage, and chronic infections owing to the inherent absorptive and secretory properties of the gastrointestinal segments (1–3). Given the limited success and high morbidity with current treatment options, tissue engineering (TE) has been considered as a novel treatment approach. The regeneration of bladder tissue derived from the patient's own cells may represent an attractive option particularly for patients of pediatric urology. The pediatric population presents several opportunities for the application of TE, as the regenerative capacity is significantly greater in infants and children than in adults. However, the specific needs of the pediatric population, primarily the need for living functional tissue replacements with a good growth potential and a long life span need to be addressed.

First attempts to replace bladder tissue by synthetic materials were performed in the 1950s, where plastic urinary bladder substitutes were implanted into patients (4, 5). The first biomaterials

used for reconstruction of the urinary bladder for clinical applications were gelatin sponge (6, 7), cellular collagen biomatrix (8) resin sprayed paper (9), bovine pericardium (10), and dura (11). However, due to unsatisfactory postoperative results this technique was suspended.

The urinary bladder possesses a unique anatomy, allowing for repetitive expansion, and contraction and withstanding the urine pressure. Furthermore, the bladder is lined with a highly specialized multilayer epithelium, the urothelium, which acts as a tight urine barrier (12). The complexity of this structure poses a challenge for regenerative medicine. During the last two decades, TE has become a rapidly growing field of research in biotechnology and medicine. It is driven by the fascinating idea of generating autologous tissue substitutes for the treatment of tissue defects and organ failure. Several animal studies have shown promising results in bladder TE. The concept of TE involves the integration of various interacting components: the applied cells need to be held together by a tridimensional scaffold which provides the shape and initial mechanical strength, and molecular signals need to induce tissue regeneration *in vivo*. There are two common approaches in bladder engineering. The acellular approach includes the use of natural or synthetic biomaterials to enhance the body's natural growth to regenerate and repair itself (13). In the cellular approach, the removed donor tissue is dissociated into individual cells, either mechanically and by enzymatic digestion. Subsequently, the functional cells are either directly implanted into the host or seeded on a suitable biomaterial after expansion in culture and thereafter implanted into a non-functional site of the bladder (14).

Several cell based approaches (15–17) in different animal models (18–20) were successful with the formation of native tissue-like epithelialization and progressive muscle and blood vessel formation (21). Atala's group created engineered bladder tissue in a canine model using autologous cells and showed functional and anatomical characteristics of a normal bladder (3, 22). In a first clinical study human bladder was engineered for patients (aged 4–19 years) with end-stage bladder disease by isolating patient's autologous bladder urothelial and muscle cells, expanding the cells *in vitro*, and seeding them on a biodegradable collagen-polyglycolic acid scaffolds. The implanted composite engineered bladders were reported to show sustainably improved functional parameters (23). However, the majority of treated patients did not achieve good bladder capacity and compliance, but developed fibrosis of the artificial bladder wall. A recent phase II study (24), using an autologous cell seeded biodegradable composite scaffold for augmentation cystoplasty in children with spina bifida did not provide improved bladder compliance or capacity. Even though these two clinical trials were similar in design and used the same cell types, the differences in cell number, type of biomaterial, or surface area grafted and type of surgery might have influenced the outcome. To date, clinical translation has failed to establish a reliably effective treatment. Various hurdles such as early tissue fibrosis, lack of vascularization, insufficient urine barrier and inadequate contractibility are challenges encountered in regenerative medicine (25, 26). In this review, we discuss the major achievements and challenges in bladder tissue regeneration and focus on different strategies to overcome obstacles.

## CELLULAR APPLICATION IN TISSUE ENGINEERING

Autologous cells are a perfect match for bladder engineering as they don't provoke inflammation and immune rejection, which are adverse effects of non-self donor cells. They can be derived from bladder tissue or from stem cells of another origin, such as the bone marrow or adipose tissue, however research in this regard is still less advanced (**Table 1**). Urinary bladder is a hollow organ composed of smooth muscle, urothelium, lamina propia, extracellular matrix, nerves, and vessels. Since detrusor muscle and urothelium represent the main properties of the bladder, the main focus of attention for bladder engineering was directed toward cells originating from these two tissues. Normal human bladder urothelium and muscle cells have been isolated from biopsies, expanded in culture, and characterized regarding differentiation characteristics and other biological functions (15, 42–44). The successful use of autologous cells for human bladder engineering derived from patients with end-stage bladder disease was shown by Atala et al. (23) and Joseph et al. (24). However, the use of autologous cells presupposes the availability of viable cells devoid of any genetic defect within the damaged or diseased tissue. In case of infection, altered tissue composition or malignancy, the adult autologous cells may be abnormal. Moreover, biopsies can lead to several problems including donor site morbidity, limited sample size, restricted proliferation ability, and loss of contractile phenotype of the cells during *in vitro* culture and expansion (45).

Smooth muscle cells (SMCs) play an important role in the functionality of the bladder and both good proliferation potential and contractile function are essential for successful tissue regeneration. Unfortunately, even mature SMCs isolated from healthy sources have shown limited proliferation capacity and loss of the contractile phenotype followed by a change to a synthetic form during *in vitro* expansion (45). The phenotypic switch between a synthetic (proliferative) or contractile (quiescent) but active phenotype can occur reversibly and transiently *in vitro* and *in vivo* (46, 47). SMCs derived from neuropathic bladders have been shown to retain their pathological characteristics *in vitro* (48). Therefore, to overcome these limitations, embryonic (27), adult, and induced pluripotent stem cells (49) have been considered for bladder engineering.

In order to create clinically applicable engineered bladder tissue using stem cells, distinct selection criteria such as accessibility with minimal invasiveness, the ability to yield large number of cells in a limited time frame, only minor changes during *in vitro* culturing, reproducibility with a high differentiation potential are mandatory. Therefore, the type and quality of stem cells for bladder engineering are critical factors.

Embryonic stem cells (ESCs) can be isolated from the blastocyst inner cell mass. They are pluripotent cells with the ability to differentiate into any cell type and with an unlimited expansion potential *in vitro* (50, 51). Recently, ESC

**TABLE 1 |** Bladder tissue regeneration with cell therapy in human and animals.

| Study | Cell types | Biomaterial | *In vivo* model | Remarks |
|---|---|---|---|---|
| Atala et al. (14) | UC | PGA | Mouse Implantation into mesentery, omentum, retroperitoneum | Successful harvesting, culturing, and seeding of UC. |
| Cilento et al. (15) | Human bladder UC | PGA | Mouse Subcutaneous implant | Formation of multilayered structures |
| Yoo et al. (22) | SMC, UC | BAM | Beagle dogs Cystoplasty | Normal bladder compliance and increase in capacity compared with unseeded controls |
| Oberpenning et al. (3) | Autologous SMC, UC | PLGA coated PGA | Beagle dogs Cystoplasty | Normal capacity, elastic properties, and histologic architecture of the bladder wall. |
| Schoeller et al. (18) | UC | Silicon | Rat Cystoplasty | Successful use of vascularized prefabricated flaps for cystoplasty in animals with better survival rate compared to control groups. |
| Lai et al. (17) | Human SMCs from normal, exstrophic. neurogenic bladders | Unwoven PGA | Mouse Subcutaneous implant | Engineered muscle from normal and diseased bladders retain their phenotype *in vitro* and *in vivo* with the same degree of contractility regardless of their origin. |
| Fraser et al. (19) | Pig UC | Polyglactin carrier meshes and deepithelialized autologous colon | Minipigs Cystoplasty | Significant contraction and poor urothelial coverage. |
| Lakshmanan et al. (27) | hEG, SMC, UC | SIS | None | Co-cultured hEG cells grew well *in vitro*. |
| Frimberger et al. (28) | Human ESC SMCs, UC | SIS | Rat Cystoplasty | Improved regeneration of the ESC-seeded grafts compared to unseeded SIS. |
| Chung et al. (29) | BMSC | SIS | Rat Cystoplasty | More rapid tissue reconstitution compared to unseeded controls. |
| Jack et al. (30) | Human PLA cells | - | Rat, mouse Injection into urethral and bladder wall | Smooth muscle regeneration and phenotypic differentiation |
| Zhang et al. (31) | BMSC | SIS | Dog Cystoplasty | BMSC-seeded SIS scaffold promoted bladder regeneration. |
| Atala et al. (23) | Autologous UC, SMC | PGA | Human Cystoplasty | The engineered bladders showed improved functional parameters over a short period (10 months). |
| Jack et al. (32) | Human ADSC | PLGA | Rat Cystoplasty | Short-term improvement in physical properties of engineered bladder tissue. |
| Sakuma et al. (33) | Adipocytes | - | Mouse Injection to the cryo-injured bladder wall | Adipocytes differentiated into SMC lineages and contributed to the bladder wall regeneration. |
| Bodin et al. (34) | USCs | bacterial cellulose polymer | Mouse Subcutaneous implant | Differentiated USCs expressed urothelial and SMC markers. |
| Adamowicz et al. (35) | BMSC | Human amniotic membrane /tachosil sponge | Rat Cystoplasty | Formation of an autonomic SMC population poorly integrated into the bladder wall. |
| Horst et al. (36) | SMC | PLGA/BAM Hybrid scaffold | Rat Cystoplasty | Bladder regeneration with improved bladder architecture (urothelium, smooth muscle and collagen rich layers, micro vessels) in hybrid compared to BAM only scaffolds. |
| Imbeault et al. (37) | DF, HUVEC, UC | DF sheets | Mouse Subcutaneous implantation | Good vascularization, with capillary-like structures in the whole thickness of the tubes. |
| Joseph et al. (24) | Autologous SMC, UC | Polyglycolide/polylactide mesh | Human Cystoplasty | Cell seeded scaffold did not improve bladder compliance or capacity. |
| Horst et al. (38) | SMC | PLGA/BAM Hybrid scaffold | Rat Cystoplasty | Increased porosity enhanced cell proliferation *in vitro* and tissue ingrowth *in vivo*. |
| Lee et al. (39) | USC | heparin-immobilized bFGF-loaded scaffold | Rat Cystoplasty | Cell seeded scaffolds significantly increased bladder capacity, compliance, regeneration of smooth muscle tissue, multi-layered urothelium. |
| Zhe et al. (40) | ADSC | BAM | Rat Cystoplasty | Morphological regeneration of the bladder smooth muscle and nerves. Improvement of bladder capacity. |
| Horst et al. (41) | SMC | Polyesterurethane/BAM Hybrid scaffold | Rat Cystoplasty | Bladder tissue formation with excellent tissue integration and low inflammatory reaction. |

*ADSC, Adipose derived stem cells; BAM, pig bladder derived acellular; BMSC, bone marrow stem cells; DF, Dermal fibroblasts; ESC, Embryonic stem cells; EnSCs, Endometrial stem cells; hEG, Human embryonic germ cells-derived stem cells; HUVEC, Human umbilical vein endothelial cells; PGA, polyglycolic acid polymer; PLA, Processed lipoaspirate; PLGA, poly lactic-co-glycolic acid; SIS, porcine small intestinal submucosa; SMC, smooth muscle cells; UC, Urothelial cells; USC, Urine-derived stem cells.*

were differentiated to mesenchymal like stem cells (MSCs) by differentiation with growth factor cocktails and supporting feeder cells (OP9) (52). ESC can be induced to become SMCs under retinoic acid treatment, expressing SMC gene markers (53–55). Therefore, they are a valuable tool to study the differentiated SMC and to test their response to therapeutic agents. In a recent study using a rat model, MSCs derived from human ESCs were shown to more effectively improve the contractile function and the potential to repair the histological injury in interstitial cystitis/bladder pain syndrome than adult bone-marrow derived cells (56). The co-culture of human ESCs with bladder SMCs and urothelium seeded on porcine small intestinal submucosa (SIS) generated viable grafts *in vitro* (27). In a follow up study, the same construct was used to augment a previously injured rat bladder, resulting in an improved regeneration of the ESC-seeded graft compared to unseeded SIS (28). However, several safety issues such as the formation of teratoma, potential immune reactions, and the risk of differentiating into unwanted cell types limit their applicability for bladder engineering.

The ability of adult stem cells to differentiate and self-renew makes them a suitable source for bladder engineering. The adult stem cells can be isolated from virtually every tissue and organ type in mammals (57). Several adult stem cell types with different availabilities are currently used for bladder bioengineering, including adipose derived stem cells (ADSCs) (58), bone marrow stem cells (29), endometrial cells, menstrual blood cells and urine derived stem cells (UDSCs).

Human ADSCs have several advantages in TE applications due to their mutipotency, ease of access and high proliferative potential. They can be isolated either from subcutaneous fat tissue biopsies or by liposuction; both procedures are less invasive and painful than bone marrow aspiration. Human ADSC have surface antigens similar to MSCs derived from human bone marrow stromal cells (58). Several studies have shown efficient differentiation of ADSCs to SMCs and urothelial cells when placed in specific induction media (59–61). In a rat model, Jack et al. (30) delivered human processed lipoaspirate cells into the bladder and urethra. The cells remained viable for up to 12 weeks, showed evidence of incorporation into the recipient smooth muscle and differentiated with time (30). Enhanced bladder architecture and function was observed in small animal models upon ADSC injection (62) or in combination with an acellular scaffold (63). Moreover, in another study on a rat model, bladder acellular matrix (BAM) seeded with ADSCs showed enhanced detrusor muscle and neuronal regeneration, as well as improved bladder capacity (40). Furthermore, human ADSCs were differentiated into SMCs with smooth muscle inductive media and grown on PLGA scaffolds in a athymic rat model for bladder regeneration. The organ bath results demonstrated smooth muscle contraction of the seeded implants but not the acellular implants after 12 weeks *in vivo* (32). Moreover, human mature adipocyte derived cells could be differentiated into SMCs and contribute to the regeneration of the bladder wall (33).

Bone marrow derived MSCs (BM-MSCs) or stromal cells possess a self-renewal capacity and a potential to differentiate into the myogenic lineage. They are easily isolated due to their tendency to readily adhere to plastic culture dishes (64). Upon induction with TGF-beta1, they can differentiate to SMC, characterized by the expression of specific contractile proteins including alpha-SMA, calponin and SM-MHC (65). In some studies, BM-MSCs were evaluated as an alternative to bladder SMCs when healthy bladder tissue was unavailable (31). An *in vivo* study in a rat model showed that amniotic membranes seeded with BM-MSC could regenerate detrusor muscle and urothelium in the bladder wall but with no proper urinary bladder function (35). In a similar study performed by Chung et al., BM-MSCs seeded on SIS showed rapid cellular regeneration of bladder constituents morphologically, presenting a possible solution to overcome the fibrosis occurring in unseeded SIS bladder augmentations (29). A similar study in a canine hemicystectomy model using BM-MSC seeded SIS for augmentation demonstrated effective bladder regeneration with solid smooth muscle bundles throughout the graft (31). Although a few studies showed formation of smooth muscle using BM-MSCs in preclinical studies, its clinical application in bladder engineering is limited, due to the low isolation yield, difficulties in harvesting and expansion, and last but not least the painful collection procedure.

## BIOMATERIALS

The complex anatomy and function of the urinary bladder pose unique challenges for the selection of scaffolds, cell types and cell sources for its bioengineering. The scaffold plays a key role in tissue regeneration and in re-establishing the biological function of the bladder tissue. Among the characteristics of the biomaterial determining the success of tissue regeneration are biocompatibility, biodegradability and scaffold architecture (66). In addition, an ideal scaffold for bladder TE should provide a microenvironment that promotes cell adhesion and a tissue organization similar to the native tissue (3, 67–71). Furthermore, the construct should serve as a barrier to urine, to protect the underlying tissue from the cytotoxic urine (72–74). It should display appropriate mechanical properties to sustain the mechanical forces necessary for bladder filling and emptying. Furthermore, the scaffold must be biodegradable at the proper rate to optimize integration into the bladder without triggering inflammation and foreign body reaction (70, 75). A special challenge ensuring regeneration and long term survival of the tissue *in vivo* is an adequate vascularization allowing for adequate oxygenation and nutrition of the regenerating tissue (76, 77). Scaffold materials for urologic tissue regeneration that are currently being investigated and have shown promise in clinical applications are mainly naturally or artificially derived biodegradable materials.

Acellular matrices are chemically and mechanically decellularized matrices such as BAM (78) and porcine SIS (79, 80). These collagen-based scaffolds have the advantage to maintain inherent bioactivity and feature the tridimensional architecture of the native tissue (81). The acellular matrices have been applied both preclinically (22, 79, 82, 83) and clinically (8, 84) with different outcomes (8, 23, 85). Major disadvantages of natural acellular matrices are the variability in physical and

biochemical properties among batches (86, 87), the alterations of the physiological environment due to decellularization and sterilization processes (71, 88) and the possible triggering of an immune response (83, 89).

Similar to acellular matrices, naturally-derived polymers like collagen or silk, produced in a number of configurations and densities, provide distinct properties mimicking the structural and mechanical properties of native tissue extracellular matrix (ECM) while being biodegradable. They have shown great promise in a number of models of TE for regenerative medicine in numerous medical applications (90–96).

Collagen Type I, a ubiquitous structural protein, has been studied extensively as a possible scaffold in soft tissue TE applications (97). Collagen has already been approved by the FDA (Food and Drug Administration). It is bioactive, does not provoke immune responses and can easily be extracted from animal and human tissues (90, 92). However, hydrogel scaffolds from collagen offer only limited mechanical strength and different methods such as crosslinking (98), ultracentrifugation (99), or evaporation methods (100) are needed to produce high concentration collagen scaffolds. More recently plastic compression of the collagen hydrogel has been applied in different fields of TE and regenerative medicine e.g., for urinary bladder regeneration (92, 93). In this cell-independent technique developed by Brown et al. (101) and (102), excess water of the collagen hydrogel is removed via mechanical compression. This enables the fabrication of denser and stronger 3D nano- and micro-scale structures as compared to conventional gels (101). Promising preclinical results with compressed collagen scaffolds in TE suggest a potential for these constructs to be used as scaffolds for bladder tissue regeneration (92).

Silk fibroin (SF), another naturally derived material, has been proposed as biomaterial for soft tissue engineering owing to its versatility and biocompatibility (91, 103). Derived from Bombyx mori cocoons, this protein based polymer addresses many of the mechanical characteristics required for urologic TE applications (91, 96). Preclinical research involving SF scaffolds in urinary tissue regeneration has been encouraging as robust regeneration of smooth muscle and urothelium have been demonstrated (94, 95). SF scaffolds in combination with seeded bladder or mucosal cell populations are a promising strategy for engineering of functional urethral tissues (96).

Synthetic polymers are rapidly gaining ground as scaffold materials. In urologic TE, biodegradable synthetic biomaterials with appropriate mechanical properties for soft tissue regeneration such as poly (lactic-co-glycolic acid) (PLGA), polyurethane (104, 105), and poly(ε-caprolactone)/poly (L-lactic acid) (PCL/PLLA) (106) have found their application. Their main advantage is the manufacturing process which allows for suitable features of micro-nanostructure, strength and degradation in a constant quality and even on a large scale. Problems related to tissue harvesting are avoided with the use of these materials. However, none of these materials convinced *in vivo*. Disadvantages of synthetic polymers are their biological inertness and the lack of the molecular signals that are relevant for directing cell activity and fate. Furthermore, they can induce foreign body reaction, and degradation may produce acidic byproducts that may affect the local microenvironment of the regenerating tissue, causing inflammation and cell death (107, 108). Unfortunately, no single biomaterial or cell source provides all the desirable properties for successful urological tissue regeneration. Current technologies in bladder TE have been hampered by an inability to efficiently initiate blood supply to the graft, ultimately leading to complications that include graft contraction, ischemia, and perforation. These deficiencies therefore necessitate the evaluation of new strategies combining the gained knowledge to closer fulfill these requirements.

## STRATEGIES TO SUCCEED

The reason for tissue engineering a whole or partial bladder is to be able to deliver a functional substitute. Since the bladder wall is subjected to mechanical forces during filling and emptying cycles (109) selection criteria for cells and biomaterials are specific. Furthermore, in the pediatric population, a living functional tissue replacement with a good growth potential and a long life span is of main concern. To this end, the use of adult stem cells is given the most attention. Ideal stem cells need to be accessible with minimal invasiveness, have the ability to expand in a short period, and maintain a stable phenotype, while not changing during *in vitro* culturing but having a high differentiation potential. Therefore, the type, quality and quantity of stem cells for bladder engineering are critical factors.

Besides the already mentioned ESC (110), ADSC (58), and BM-MSCs (29) an other suitable stem cell candidate for urological tissue reconstruction are USCs. They can be isolated from voided urine within 24 h after urine collection (34, 111). USCs show MSCs characteristics and can be differentiated to SMCs, expressing all SMC lineage specific markers (111) with contractile function comparable to native SMCs (112). Originating in the urinary tract system, USCs are suggested as a good stem cell source for bladder TE with the benefits of simple, safe, low-cost and non-invasive collection technique (34). It was demonstrated that a USCs can differentiate in porous bacterial cellulose scaffolds, which may assist in the development of an engineered urinary conduit (34). Furthermore, it was shown that human USCs seeded scaffold-heparin-bFGF grafts improved biocompatibility, increased bladder capacity and compliance, as indicated by smooth muscle and urothelium layer in a partial cystectomy rat model (39).

In addition, a few studies showed that endometrial stem cells, which are of mesenchymal origin, can differentiate to SMCs and are suitable for bladder engineering (113). These cells can be harvested from the endometrium by two methods: either by an endometrial biopsy from the uterus or by collection of menstrual blood. In contrast to bone marrow and adipose tissue cells, for which at least a local anesthesia is required, these cells can be harvested without any anesthetic procedure (114). Furthermore, endometrial stem cells could also differentiate into urothelium using keratinocyte and epithelial growth factors, and in combination with 3D-silk-collagen they could serve as a suitable scaffold for building urinary bladder wall in females

(115). However, endometrial-derived stem cells have not yet been used in any *in vivo* study.

Recent reports have shown that induced pluripotent stem cells (iPSCs) may answer the need for alternative cell sources for bladder regeneration. The iPSCs are reprogrammed, terminally differentiated somatic cells which have developed ESC-like cells characteristics following expression of various pluripotency transcription factors (116). Theoretically, iPSCs can produce an unlimited number of differentiated cells for autologous cell therapies (117). With this approach a patient's cells may be directed to become iPSCs and subsequently to differentiate and repair tissue. However, safety and efficiency is still under investigation. SMCs generated from iPSCs were shown to acquire contractile features and express contractile proteins (118, 119). Moad et al., for the first time, generated iPSCs derived from human urinary tract cells (bladder and ureter) which offers a potential for bladder engineering and *in vitro* studies (49). However, there are continuing concerns regarding induction of tumors by iPSCs. Currently discussed solutions include modifications in induction methods toward virus-free, transgene-free reprogramming and xeno-free systems (120, 121). In addition, the use of iPSCs requires an appropriate protocol for efficient *in vitro* differentiation, and in order to address safety issues its effect should be tested *in vivo*.

Current studies have shown that autologous cells in combination with biomaterials are the best options for bladder engineering. In addition, the construction of a three-dimensional scaffold *in vitro* before *in vivo* implantation would facilitate the terminal differentiation of the cells *in vivo*. The optimization techniques such as co-culture of different cell types and predifferentiation before implantation showed improved cells survival *in vivo* (122). Son et al. demonstrated that human dental pulp stem cells co-cultured with bladder derived SMCs or in a SMCs-conditioned medium with the addition of the transforming growth factor beta 1 (TGF-β1) can differentiate efficiently into bladder specific SMCs. This approach can be used as a less invasive alternative to harvest stem cells for smooth muscle regeneration and for bladder engineering (123). De-differentiation of SMCs from a contractile phenotype to a synthetic phenotype, which is characterized by SMCs hypertrophy and fibrosis is a known problem in bladder engineering. Methods to maintain the cell phenotype include cell culture microenvironment, the use of growth factors, the optimization of biomechanical and surface properties of the biomaterials and mechanical stimulation (47, 124).

The fabrication of hybrid or composite scaffolds consisting of at least two different biomaterials ideally allows the combination of the positive characteristics of the different compounds and even to develop new biomaterials with a wider range of physicochemical properties (36, 71). The use of hybrids of BAM and synthetic polymers has been described by our own group among others. We developed a bilayered scaffold by direct electrospinning of PLGA (36, 38) or Polyurethan microfibers (41) onto the luminal side of a BAM and demonstrated, that these scaffolds seeded with bladder SMCs supported the regeneration of a multi-layered bladder wall consisting of urothelium, lamina propria, and detrusor muscle resembling native control bladder in rats. Ajalloueian et al. combined CC hydrogels with electrospun PLGA sheets and studied the effect of different fibrillary densities on fibroblast performance (125). They showed that by decreasing the collagen content of CC hydrogel, not only a better cell environment and optimal mechanical properties are achieved, but also the application costs of this biopolymer are reduced. Another method to combine the physical properties of synthetic polymers with the biochemical as well as molecular characteristics of naturally derived scaffolds is the blending of natural and synthetic polymers as for example described by Moshfeghian et al. (126). They evaluated the formation of chitosan–PLGA blend matrices using controlled-rate freezing and lyophilization technique. By altering the freezing conditions they were able to control pore morphology and degradation kinetics of the scaffold with a positive influence on SMC spreading and colonization *in vitro*. Franck et al. produced a silk-based biomaterial coated with ECM (collagens or fibronectin), blending more than one naturally derived polymer to synthesize scaffolds for bladder tissue engineering (119). This composite scaffold was shown to be biocompatible and to support primary cultures of bladder UC, SMC, and pluripotent stem cell adhesion, proliferation, and differentiation. Such approaches can be adapted to a number of characteristics that are appropriate for bladder augmentation including mechanical properties, permeability, pore size, degradation characteristics, and biological activity (71).

The concept of natural self-assembly of cells differs from all other TE techniques that use pre-formed synthetic scaffolds. This innovative scaffold-free technique relies on the ability of cells to produce and assemble their own ECM (127). Initially introduced for skin TE (128), this approach also enabled the reconstruction of other tissues such as blood vessel, heart valve, cornea, adipose tissue, vaginal mucosa, and urinary tissues (129). In a recent study, Orabi et al. were able to produce a multi-layered construct with histological and molecular properties similar to native tissue *in vitro*. For this approach, they used bladder-specific stromal cells from the lamina propria co-cultured with UCs or SMCs (130). However, the self-assembly technique still needs to be investigated for urologic tissue regeneration *in vivo*.

To improve the outcome of bladder regeneration, scaffolds can be functionalized with growth factors, creating a microenvironment that simulates the integration of the tissue engineered constructs (131, 132). Physiologically, growth factors are components of the ECM, which are actively released after injury. They play a crucial role in tissue repair and the prevention of fibrosis. The therapeutic use of recombinant growth factors is based on the hypothesis that through appropriate signaling they induce and/or accelerate the healing process. Several growth factors have been identified as important in the development of functional urological tissue (133), mainly vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) (134, 135). The use of VEGF alone or in combination with NGF resulted in improved bladder wall regeneration and angiogenesis (134–136). When using stem cells, the presence of appropriate growth factors is essential for cell differentiation (137, 138). In most cases, incorporation of

biologically active molecules into the scaffold material has been aimed at rapid restoration of vascular networks to maintain tissue viability and long-term survival. Growth factors are considered to be critically important modulators during all phases of tissue regeneration (71). To provide an effective delivery of growth factors, some challenges must be overcome. Because of the high instability of growth factors *in vivo*, various slow-release devices of natural, synthetic and composite materials have been designed (139, 140). Biomaterials with degradable porous reservoir structures or pre-encapsulated microspheres have been used to control effective targeting (141). For an effective long-term delivery, growth factors can be encapsulated in biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) or poly-L-lysine (PLL) (142, 143). Those systems are designed to release the loaded protein in a sustained manner following the degradation of the polymer. To improve the controlled delivery, Layman et al. developed ionic-albumin microspheres that allow the time-controlled release of two growth factors (144).

Nanoparticles have not only been used for controlled delivery of bioactive molecules and growth factors, in TE they have been used in order to improve the mechanical and biological performance of the regenerated tissue (145). For example nanoparticles can play a vital role in enhancing the mechanical properties of the scaffold as shown in skin TE, where the tensile strength of collagen or silk fibroin was improved by using TiO2 (146) or hydroxyapatite nanoparticles, respectively (147). Furthermore, nanoparticles can mimic the natural nanostructure of ECM components of tissues, and therewith influence cellular activities such as adhesion, growth and differentiation of stem cells (148, 149). Although the use of nanoparticles recently made an enormous progress, *in vivo* experimentation to verify the successful results from *in vitro* studies (150) are still needed.

The establishment of a functional vascularization represents one of the major challenges for the implementation of TE applications in clinical practice. The survival of larger and complex tissue substitutes after implantation depends on the rapid development of an adequate vascularization. Furthermore, vascularization is a major prerequisite for a complete restoration of organ structure and functionality. Classical approaches to promote vascularity in tissue substitutes focus on the stimulation of vascular ingrowth into tissue constructs by optimizing the material properties of scaffolds (38, 151, 152) or by enriching implants with proangiogenetic factors (153–155). A promising approach is the incorporation of growth factors which can be released in a time-dependent manner at the implantation site. Therefore, various slow-release devices of natural, synthetic, and composite materials have been designed (156, 157). An additional approach to supply growth factors is the use of transfected cells, which overexpress angiogenic factors (158).

Prevascularization of tissue constructs with networks of capillaries aims to accelerate functional anastomosis with host tissue upon implantation. *In vitro* prevascularization of thicker constructs and the connection to the host vasculature *in vivo* is essential to guarantee immediate supply to the cells within the construct. These requirements determine the success of the applied transplant (158, 159). However, angiogenesis in a large avascular graft *in vivo* does not occur fast enough to avoid hypoxic conditions (160). This innovative approach basically aims at the generation of preformed microvascular networks in tissue constructs prior to their implantation by co-culturing endothelial cells (ECs) with supporting cells (161). The co-culture approach is the most biomimetic option, which can be achieved by growing ECs with mural cells, such as fibroblasts (162) or SMCs (163) or MSCs (164). Also the self-assembly technique showed promising results with endothelialized substitutes for skin (165) and urethral reconstruction (37). After implantation, these networks can then be rapidly perfused with blood by inosculation with the surrounding host microvasculature (166) or by surgical anastomosis of feeding and draining blood vessels (167, 168). This enhances earlier vascularization of the graft, thus potentially decreases the risk of ischemia, necrosis and fibrosis and enhances graft regeneration and thereby long term function. As the feasibility of engineering blood vessels in bladder grafts becomes reality, inosculation and prompt nourishment of grafts upon transplantation will further potentiate the clinical use of bioengineered bladder tissue (73). However, mimicking natural vascular architecture and rebuilding microvascular networks *in vitro* is still challenging and limits clinical applications. These promising achievements lead to further advancement of these prevascularization concepts and their adaptation to individual therapeutic interventions will markedly contribute to a broad implementation of TE applications in clinical practice.

## OUTLOOK AND CLINICAL TRANSLATION

Urinary diversions made from engineered bladder tissue would remove the need for bowel tissue for bladder reconstruction. An off-the-shelf bladder tissue would revolutionize reconstructive urology and would allow a substantial reduction in morbidity and improve the long term outcome of bladder augmentation, especially in the pediatric patient. With recent advances in isolating, growing, and differentiating host stem cells, an increased understanding of the cell niche required to maintain the artificial tissue, and novel techniques for the generation of an intact blood supply, it appears that the major elements for the engineering of a functional bladder wall are achievable. Despite impressive progress in the field of bladder TE over the past decades, the successful transfer of these approaches into clinical routine still represents a major challenge. Large animal trials are necessary to confirm the applicability of the approaches in a model similar to the growing human organism to meet the special needs of this patient group.

As discussed in this review there are several strategies to overcome the hurdles of TE which lead to new approaches in bladder regeneration. In order to improve the bladder engineering for clinical application we suggest further unifications of the strategies and approaches including a collaborative effort of experts of different fields. With its complex nature and distinct mechanical properties, the development of a next generation bioengineered bladder

tissue requires the combined knowledge and techniques of material science and cell biology to be successful in future clinical application.

## DATA AVAILABILITY

The datasets for this manuscript are not publicly available because its a review. Requests to access the datasets should be directed to maya.horst@ksipi.uzh.ch.

## AUTHOR CONTRIBUTIONS

MH and SS wrote the manuscript. DE and RG authors contributed to the final version of the manuscript.

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