COMPLICATED URINARY TRACT INFECTIONS: HIGHLIGHTS ON DIAGNOSIS AND MINIMALLY INVASIVE TREATMENT

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ABSTRACT

Complicated urinary tract infection (UTI) has always been a challenging subject to diagnose and treat. New, less invasive, techniques have been introduced in the last decade with the development of the new generations of high definition endoscopes and the robotic platforms to treat the surgically correctable pathologies underlying UTIs. This review will discuss the different underlying pathological conditions for complicated UTI and their management.

Keywords: Urinary tract infection (UTI), minimally invasive, complicated, complex.

PATHOPHYSIOLOGY

Background

Complicated urinary tract infections (UTIs) are urinary infections secondary to functional or structural abnormalities of the urinary tract.[1] A UTI is the inflammatory response of the urothelium to invasion by microorganisms, commonly associated with bacteriuria and pyuria. Certain other patient factors, including an immune-compromised host or genitourinary tract manipulation, can also lead to inclusion in the term 'complicated'. Various thresholds are used to define the amount of colony forming units (CFU) required to diagnose an infection. By definition all UTIs in men are complicated and the latest EAU guidelines use a threshold of $>10^4$ and $>10^5$ cfu/ml for complicated UTI in men and women, respectively. This is higher than the value of 10^3 cfu/ml for acute uncomplicated cystitis in women.[2] The most common pathogens include *Escherichia coli*, *Enterococci*, *Pseudomonas aeruginosa*, *Candida* species, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.[3] As uncomplicated urinary infection is rare in men, any male urinary infection is usually considered complicated.[4]

The main significance of complicated UTIs is their challenging ability to resist normal treatment protocols. The pathogenesis of complicated UTI is multifactorial; they are generally caused by urine stasis, either due to obstruction (structural) or failure of emptying (functional), leading to by passing the normal host defence mechanisms with formation of nidus for infection that can be resistant to usual antimicrobial agents.[5]

Structural Abnormalities

Ureteric or urethral strictures, tumours of the urinary tract, urolithiasis, prostatic hypertrophy, diverticulae, pelviureteric junction obstruction (PUJO), renal cysts, and congenital abnormalities are all causes for urinary tract obstruction (UTO) which is the most important factor leading to complicated UTI. Overdistension will result in a residual urine pool providing a continuous medium for bacterial growth and interfering with the local mucosal defence mechanism.[1,6] Vesicovaginal fistula (VVF) and colovaginal fistula (CVF) are also a known cause of the development of recurrent UTIs.

Instrumentation

Indwelling urethral catheter, intermittent catheterisation, ureteric stent, nephrostomy tube, and urological procedures can all allow easy access of pathogens into the urinary tract, which can lead to formation of biofilms and subsequently provide a nidus, making it difficult to eradicate infections with antimicrobial agents.[1,5]

Impaired Voiding

Neurogenic bladder, spinal cord injuries, cystocoeles, vesicoureteral reflux, and ileal conduit are all factors that can lead to incomplete drainage of urine and therefore impair normal flushing of bacteria from the urinary tract, with imbalance in one of the major host defence mechanisms contributing to complicated UTI.[7]

Metabolic Abnormalities

Nephrocalcinosis, medullary sponge kidney, renal failure, and diabetes mellitus can mainly affect the host mechanisms leading to severe forms of complicated UTIs including intrarenal and perirenal abscess, emphysematous pyelonephritis (EPN) and papillary necrosis, and xanthogranulomatous pyelonephritis.[8]

Immunocompromised

Those who have had a renal transplant and patients with acquired immune deficiency syndrome have significantly impaired host defence mechanisms making it difficult and sometimes impossible to achieve an effective response to the antimicrobial agents. In complicated UTIs, less virulent uropathogens, that rarely cause disease in a normal urinary tract, can cause significant damage to the urinary tract; associations between Group B streptococcal bacteraemia, *Candida*, and *Enterococci* were identified in some studies with complicated UTIs in vulnerable patients.[9,10]

DIAGNOSIS

This diagnosis of a complex UTI is based on three main features: the clinical picture, microbiological tests, and radiological investigations. Physicians should always consider atypical microbiology and the potential for UTO, which may require prompt drainage in this patient group.

Clinical Picture

The most common clinical presentations of UTI include acute cystitis, pyelonephritis, and less commonly acute prostatitis, but patients with abnormal urinary tracts can present more atypically. A carefully taken history is an essential diagnostic tool, with particular attention to the symptoms of frequency, dysuria, haematuria, suprapubic, and/or loin pain. Focussed questioning on preceding urological complaints/surgery, any indwelling catheters/stents, history of neurological disease, and diabetes/immunosuppression are vital. It has been suggested that the acute onset of dysuria and frequency without any vaginal symptoms can have a positive predictive value as high as 90%.[11] Clinical examination is crucial to reveal features which can alert the physician to underlying urological disease, but also to enable the recognition of the acutely unwell patient who may be suffering from urosepsis, which can be clinically evident as severe infection of the urinary tract and/or the male genital tract (e.g. prostate); features consistent with systemic inflammatory response syndrome, such as fever, tachycardia, tachypnoea, and respiratory alkalosis, which were earlier considered mandatory for the diagnosis of sepsis, are now considered to be the alerting symptoms. It may be associated with multiple organ dysfunction, hypoperfusion, or hypotension.[12] If this diagnosis is made, prompt resuscitation and treatment is mandatory.

Laboratory Tests

Basic laboratory tests may reveal elevated inflammatory markers and renal function should be recorded. The urine dipstick is a simple and cheap bedside test and is very useful in confirming a diagnosis of UTI. The sample should be collected as a 'clean-catch' midstream specimen with appropriate cleaning of the glans in men, although recent reports have suggested no difference in rates of contamination between cleaned and uncleaned groups.[13] The presence of nitrates and leukocytes in the urine are strongly suggestive of infection. Most Gram-negative bacteria (the most common infective agent) convert nitrates to nitrite and this forms a pink colour in azo-dye when it comes into contact with the aromatic amine reagent of the dipstick. The specificity of this test has been reported to be as high as 100% although the sensitivity is less.[14] Leukocyte esterase is produced from neutrophils within infected urine and this also results in a colour change on the dipstick. Combining both increases the specificity but may reduce the sensitivity.

Urine should be sent for Gram stain, culture, and sensitivity. Microbiology can help provide crucial information including the identity of the infective organism and providing antibiotic sensitivities. If clinical evidence of sepsis is identified, blood culture and inflammatory markers including C-reactive protein and leukocyte count should be included in the initial investigations.[12]

Radiological Tests

In the context of a complicated UTI, imaging is used to alert the urologist to a structural problem which requires intervention. This can include serious conditions such as an infected and obstructed system, renal/perirenal abscess, EPN, and also prostatic abscess formation. Patients who show prompt clinical improvement with antibiotic treatment may not require acute imaging. However, in patients who do not improve, or if there is diagnostic uncertainty, then urgent imaging is indicated. A plain radiograph may enable visualisation of a renal/ureteric stone or intrarenal gas. Ultrasound provides a good assessment of the renal parenchyma with identification of hydronephrosis, perinephric collections, and renal abscess.[15] Computerised tomography (CT) scanning can be performed either with or without intravenous contrast. If there is a diagnostic concern, a non-contrast CT of the kidneys, ureters, and bladder is a highly effective technique to confirm/rule out ureteric colic with low dose techniques reducing the radiation exposure.[16] Contrast CT enables accurate identification of acute pyelonephritis, renal abscess, infected renal cysts, and EPN.[17] In the acute setting magnetic resonance imaging can be utilised in the presence of an allergy to iodinated contrast media used in CT and in pregnancy (after the first trimester) or if prostatic abscess is clinically suspected.[17] In the paediatric population, voiding cystourethrography can be helpful in demonstrating ureteric reflux. However it is an invasive test with significant radiation exposure and it is debate as to the predictive value of reflux in causing renal scarring.[18]

MANAGEMENT

After the initial diagnosis and antimicrobial or conservative treatment of the underlying cause of the complicated UTI, historically the next step has been an open procedure in many cases. With the introduction of new endourological techniques in the last 50 years, and the more recent introduction of laparoscopy and subsequently the robot, patient outcomes have greatly improved. It is important to remember that there are many functional causes of complicated UTIs, which is where the multidisciplinary team approach can be very useful. With the expertise of the specialist nurses, neurologists, and endocrinologists, and the development of novel clean intermittent self-catheterisation catheters, to reduce rates of bacterial colonisation, many patients can now be managed in the long term with minimal significant problems.

The introduction of flexible ureteroscopy in the 1960s fundamentally changed the way in which urologists managed upper tract calculi. Rigid and flexible ureterorenoscopy can both increase intra renal pelvic pressure and subsequent backflow, both intrarenal and pyelolymphatic. Together with potential extravasation, this can result in post-operative sepsis. A porcine model has also shown irreversible damage to the renal parenchyma due to these raised pressures.[19] There are different methods of breaking up ureteric and renal calculi with a laser fibre. For softer calculi, and to prevent the formation of multiple small fragments, the technique of dusting/painting may be used. In these cases the laser fibre is used to reduce the bulk of the stone in fine layers producing only 'dust'. A quicker method is to drill down into the calculi at multiple points thus shattering it into smaller fragments which can be removed with a basket. Finally, the term 'popcorning' refers to moving a calculi or fragment into a calyx and holding the fibre in the middle of the calyx. This technique agitates the contents of the calyx and they bounce between the fibre tip and the wall. This results in fragmentation which may obviate the need to use a basket. As technology has advanced, allowing smaller scopes and better vision, new robotic devices are currently being trialled. A preliminary study has shown that the Roboflex Avicenna significantly improves ergonomics with the next step looking at clinical outcomes.[20]

The current standard of care in cases of significant nephrolithiasis is percutaneous nephrolithotomy (PCNL) due to the relatively large calibre access sheath and higher stone-free rates than completely endoscopic techniques. In a large group, patients with urinary tract abnormalities were found to be more at risk of UTIs. These patients underwent PCNL for their stone burden and had lower stone-free rates than the normal population.[21] The trend, however, is a decrease in the size of the PCNL tract due to advances in lenses and other associated equipment. There are multiple benefits, including better preservation of renal function and reduced morbidity with similar rates of stone clearance in a selected group as standard PCNL. The recent description of ultraminiperc in literature using a 6 Fr scope through an 11 Fr to a 13 Fr access sheath, has shown 1 month stone-free rates of 97.2% when treating a group with a mean stone size of 14.9 mm.[22]

Despite the limited use of broad spectrum antibiotics impregnated stents, still some studies have proven a marked impact on biofilm formation, encrustation, or infection development. The triclosan eluting stent is an example of those that have led to significant reductions in several common ureteral-stent-related symptoms and UTI incidence.[23,24]

A VVF can be an unusual cause for recurrent UTIs especially after pelvic surgery and the administration of pelvic radiotherapy. In the first instance conservative management can be undertaken, with the insertion of a urethral catheter and the administration of antibiotics in small VVFs, allowing the fistulous tract to close by its own volition. However, many cases do proceed to surgery and traditionally have been performed as open procedures using an omental flap to prevent the fistula from recurring. With the advent of robotic surgery and its increasing use in the urology and gynaecology arenas, more complex operations are able to be carried out minimally invasively. There is published evidence of repairing high VVFs with a peritoneal flap inlay.[25] Certainly in comparing minimally invasive and open surgery in patients with recurrent VVFs, there is no difference in success rates but there is a reduced morbidity and decreased hospital stay in the robotic-assisted laparoscopic group.[26] The next evolution has been the trial of laparoendoscopic single-site surgery in this group with decent early results.[27] It follows that robotic surgery has also been shown to be feasible in the treatment of CVFs after prostatectomy.[28]

Ureteric reimplantation for vesicoureteric reflux in children has historically been performed via an open procedure due to the lack of intra-abdominal space, meaning laparoscopy alone has not been a viable option. With the instrument articulation allowed by the robot, the role for minimally invasive surgery has come to the fore. In a small group, robotic assisted ureteric reimplantation has been shown to be a feasible procedure with satisfactory outcomes.[29]

There are a number of options in the definitive management of PUJO. Endoscopically, retrograde laser (Holmium-YAG) endopyelotomy has respectable success rates documented at 77% in cases of primary PUJO.[30] Currently, the gold standard is robot-assisted laparoscopic pyeloplasty (RLP) for both primary and secondary PUJO. A large, multicentre study has shown the benefits of RLP over the conventional laparoscopic approach. Success has been shown in 96% at nearly 4 years with overall low complication rates (6.6%) and short hospital stay.[31]

The daVinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA) and newer endoscopic robots such as the Roboflex Avicenna have, and will, play an integral part in the future of urological practice. The daVinci robot has been shown to reduce hospital stay and allows greater dexterity when compared to laparoscopy in certain cases. One must, however, bear in mind the associated costs, particularly with newer robotic technologies, and weigh this up with any decision making. With the advent of robotic technology, telementoring and remote operating have developed greatly in recent times and have been used to help clinicians attenuate their learning curve when picking up this new skill. Telementoring has also been shown to be of great benefit in the training of urology trainees.[32]

CONCLUSION

Minimally invasive techniques have long played an integral role in the diagnosis and treatment of many urological conditions. With developments in technology, robots are more accessible and subsequently being employed for a wider variety of procedures. Recent reports have described that the administration of antibiotics in primary care and hospitals are on the rise, leading to increased levels of antibiotic resistance. Therefore, addressing the cause of complicated UTIs is of paramount importance and if they can be managed via a minimally invasive approach, the patient will benefit from lower morbidity and potentially better outcomes.

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