

REVIEW ARTICLE



Sepsis in urology – where are we now? And where are we going?

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ABSTRACT

Context: There has been heightened public awareness of the important issue of sepsis in the lay press in recent years with a focus on rapid detection and treatment. Within the field of Urology, how good are we at identifying, preventing and managing sepsis?

Review: Reducing the morbidity and mortality associated with sepsis requires a multi-faceted approach including heightening awareness, prevention, early recognition of deterioration, escalation of care when necessary, implementation of antibiotic stewardship and the development of novel antimicrobial treatment strategies.

Discussion: We review some of the aspects of sepsis management within our field that are working effectively and others that could potentially be optimised.

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is a significant burden on society due to its high morbidity, mortality and resource use. In 2017, an estimated 11 million people lost their lives due to sepsis [1]. The in-hospital mortality rate is estimated at between 20 and 45% [2], and sepsis consumes almost half of our intensive care unit resources [3].

Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs [1]. There are inherent risks of bacteriuria, urinary tract infection and urosepsis associated with many urological conditions. Findings from the Global Prevalence of Infection in Urology (GPIU) study have consistently demonstrated that the prevalence of hospital acquired urinary tract infection (HAUTI), is approximately 10% [4] across urology inpatients, however the prevalence of urosepsis has increased across this cohort from approximately 15% in 2003 to 25% in recent years [5].

Whilst our speciality has been to the forefront of much contemporary surgical innovation, it is current track record in relation to the prevention and management of urosepsis has been much less prominent or effective. We review some of the aspects of sepsis management within our field that are working effectively and others that could potentially be optimised.

Awareness

Unfortunately despite its prevalence, sepsis fails to command a large international profile. The United Kingdom is one of only 3 countries where sepsis awareness is reported as being

above 50% amongst the general population [6]. This lack of awareness is sited as a major contributory factor to the continuous rise in incidence of sepsis [6].

There have been numerous public health campaigns which have looked to affect this, but the majority have been without significant success. The 'Just ask: "Could it be sepsis?"' campaign developed by 'The UK sepsis trust' is touted as one of the more successful on account of its tailored, environment specific approach to heightening awareness [6]. Instead of looking at sepsis as a unique entity, the campaign focussed on the role it plays within society and how individuals are affected in a variety of different contexts.

When we consider individuals with urological conditions, perhaps sepsis education could be targeted at specific cohorts with known higher rates of incidence. From known stone formers to those with indwelling catheters to those undergoing elective procedures, there are a number of patient groups that would likely benefit from sepsis education being integrated in to their standardised care plans. It is important also, that patients are educated in relation to some of their own personal inherent risk factors that may place them at increased risk of developing infection. Diabetic patients for example or those who are immunosuppressed, should be well versed as to their inherent risk. Through furthering patient engagement and understanding, both clinician and patient can be better equipped to recognise and manage this all too common complication.

Risk identification

Risk management for healthcare entities can be defined as an organised effort to identify, assess, and reduce, where

appropriate, risk to patients, visitors, staff and organisational assets [7]. With reference to sepsis in urological patients specifically, risk identification is a complex process that encompasses early identification of individuals at higher risk, but also early identification of those who are deteriorating due to the presence of infection.

Risk factors

There are a vast number of potential contributory factors, to the development of infection in urological patients. Broadly these factors can be categorised into endogenous and exogenous risk (Figure 1). Put simply, these are inherent factors prevailing within a patient prior to their engagement with a urology service, and those which we convey upon our patients. It is critical as urologists that we are aware of a patient's endogenous risk, prior to exposing them to exogenous risk. Both must be considered carefully in advance of intervention.

Endogenous risk factors

Endogenous risk factors, are a consequence of co-morbidity, organic dysfunction or anatomical abnormality. Age and immunodeficiency are well established risk factors for the development of infection. Diabetes mellitus is of particular importance when we consider urological patients, as diabetics are more likely to have asymptomatic bacteriuria and urinary tract infection [8]. Bacterial colonisation and the factors that affect the location and spectrum of organism are also critically important. Recent hospitalisation, antibiotic use, prolonged catheterisation and the presence of urinary tract calculi have all been associated with increased rates of HAUTI [9]. Similarly the presence of anatomical abnormalities leading to altered microbial flora or urinary stasis can increase prevailing level of risk.

Exogenous risk factors

Exogenous risk factors are those that are introduced into a patient for one reason or another which convey direct risk of infection. The urinary catheter is the most common example but others include nephrostomy tubes, pigtail drains and of course instrumentation and surgical intervention. Duration of exposure is the most important related factor. With reference to urinary catheters, UTI's relating to short periods of catheterisation are usually single organism infections. Long term catheterisation can result in biofilm formation and encrustation and is associated with multi-strain colonisation and infection [10]. In turn these infections are often more complicated and difficult to treat effectively.

Evaluating the likely risk associated with a specific urological intervention can be complex. Grabe et al. [11] described a tentative list of criteria for assessing contamination levels for common urological procedures. The classification method is based on the traditional system used in open surgery and considers factors such as approach, whether the urinary or gastrointestinal tracts are opened and level of

emergency, to determine whether the case is likely to be considered clean, clean-contaminated, contaminated, dirty etc. This is useful in that it helps collaborate important procedure specific risk factors to allow the clinician gather an idea of the level of potential risk associated with a procedure. It is critical as clinicians, that the prevailing infection risk of each prospective patient is understood and evaluated in advance of instrumentation or surgical intervention. A structured objective approach to patient assessment such as that suggested by Grabe et al. [11] may be of benefit, allowing better identification of those at greater risk, in advance of exposing them to exogenous risk factors.

As a result prophylactic measures can be undertaken to minimise potential risk, facilitating a reduction in the numbers that may progress to develop sepsis.

Early warning scores

Introduction of scoring systems (NEWS 2, MEWS, PEWS) based on clinical parameters are validated and well established in current clinical practice. They have been proven to improve outcomes across a variety of specialties and international settings [12]. Systemic inflammatory response syndrome (SIRS) describes a serious condition in which there is inflammation throughout the whole body. It may be caused by a severe bacterial infection (sepsis), trauma, or pancreatitis. It is marked by fast heart rate, low blood pressure, low or high body temperature, and low or high white blood cell count [13]. The SIRS criteria will be familiar to many of us in clinical practice, and has been adapted universally to help clinical teams identify patient deterioration promptly.

The qSOFA score is a bedside prompt that may identify patients with suspected infection who are at greater risk for a poor outcome outside the intensive care unit (ICU). It uses three criteria, assigning one point for low blood pressure (SBP \leq 100 mmHg), high respiratory rate (\geq 22 breaths per min), or altered mentation (Glasgow coma scale $<$ 15) [1]. The current evidence suggest the qSOFA may be a more sensitive score for determining those patients more likely to require critical care input (Figure 2).

There is evidence that the prediction value of generic early warning scores suffers when compared to specialty-specific scores, and that the sensitivity of such tools can be improved by the addition of other variables [12]. Only 1 in 5 nosocomial urinary tract infections will occur in the absence of any 'classic' UTI predisposing factors [15]. The evidence here suggests, integration of such risk factors into a specialty-specific early warning score for urological patients would likely be beneficial. Requisite risk factors must be easily identifiable, quantifiable and accurate in determining those at greater risk.

Early identification of infection

Sepsis prevention relies on timely identification and prompt treatment of infection. Understanding the pathophysiological mechanisms behind sepsis and more specifically urosepsis is important. In brief, sepsis is initiated when pathogen or

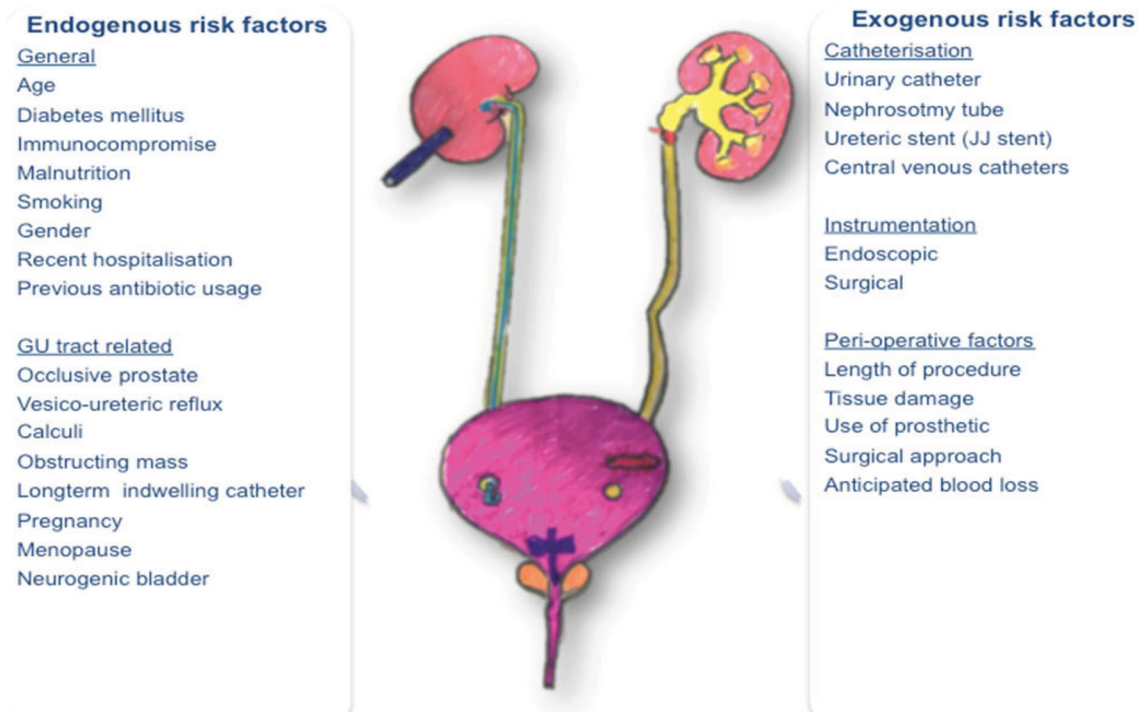


Figure 1. Risk factors for the development of infection in urological patients.

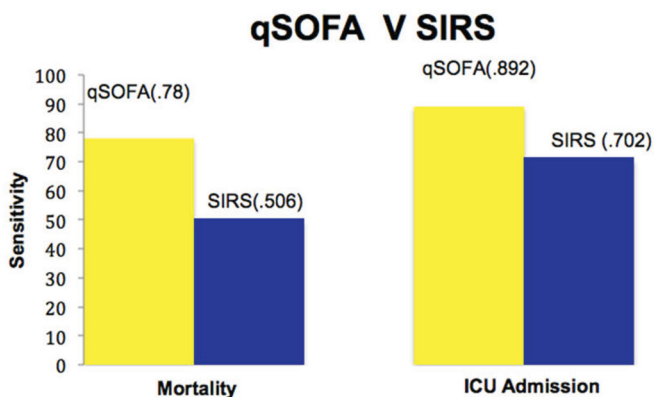


Figure 2. qSOFA Vs SIRS: sensitivity in predicting mortality and ICU admission in patients with sepsis [14].

damage-associated molecular patterns recognised by receptors of the innate immune system generate pro-inflammatory cytokines. A transition from the innate to the adaptive immune system follows until an anti-inflammatory response predominates, leading to immunosuppression. Much research has focussed on identifying novel markers with the propensity to allow earlier more accurate detection of infection. Procalcitonin is the inactive subdivision of calcitonin, it has been found to be an effective marker in discriminating between sepsis and severe sepsis [16]. Its clinical application remains somewhat controversial, though there is strong evidence supporting its role in distinguishing bacterial from other types of infection in the critical care setting, leading to more adequate diagnosis and treatment [17].

The major shortcoming of traditional culture-based approach to microbial identification, is the associated delay in diagnosis. Real time polymerase chain reaction (PCR)

analysis kits are likely to represent the future. Novel tests such as the Sepsis@Quick test have demonstrated superiority to blood cultures not only in time to result but also range and accuracy of pathogen identification [18]. Additionally the Sepsis@Quick test has been associated with a reduction in sepsis-related mortality [18].

Management

The key principles of sepsis management are after recognising early signs of sepsis, appropriate blood and urine cultures are taken before simultaneous fluid resuscitation and prompt administration of empirical anti-microbial agents. The Surviving sepsis campaign provided us with the 'Sepsis six', a clear, stepwise approach to investigating and managing patients with suspected sepsis. The 'Sepsis six' has revolutionised the international approach to sepsis management and has highlighted how early recognition and management can greatly improve a patient's chances of survival [19].

Sepsis-6

- Administer high flow oxygen.
- Take blood cultures.
- Give broad spectrum antibiotics.
- Give IV fluid challenges.
- Monitor serum lactate and haemoglobin.
- Accurately measure hourly urine output.

Anti-microbials

Antibiotic stewardship is defined as 'the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention

of infection, whilst minimising patient toxicity and future impact on subsequent resistance [20]. Antibiotic stewardship continues to be of paramount importance, however it is critical that important findings from GPIU studies are not discounted [21]. The evidence here suggests the spectrum of pathogen and resistance rates for other HAUTI's was not representative of that found in patients with urosepsis [21]. It is important that we continue to select broad spectrum empirical antibiotics as per local hospital guidelines as part of our initial management of patients with suspected urosepsis. The evidence suggests early narrowing of the spectrum without awaiting results of relevant cultures, could have detrimental effects on mortality rates and patient outcomes. This said, delays in follow up of culture results, and subsequent delays in alteration of antibiotic therapy, have contributed massively to the noticeable increase in rates of antibiotic resistance. We must endeavour to liaise closely with our microbiology and infectious disease colleagues to help curb this surge in resistance. Individually and collectively we need to have an up to date knowledge of both local and individual patient antimicrobial resistance patterns before implementing prophylactic or treatment agents. Prior to embarking on any invasive intervention on the urinary tract, results of a recent urine culture should be known. Ensuring that such results are available when required can be challenging for the patient, the urologist and their institution. Preoperative assessment and admission pathways involving all stakeholders that facilitates this practice should be formed and implemented. The growing problem of antimicrobial resistance means that the search for non-antibiotic alternatives for the treatment and prevention of UTI is of critical importance. Potential nonantibiotic measures and treatments for UTIs include behavioural changes (increased fluids), dietary supplementation (herbal medicines and cranberry products), NSAIDs, probiotics, D-mannose, methenamine hippurate, oestrogens, intravesical glycosaminoglycans, immunostimulants, vaccines and inoculation with less-pathogenic bacteria [22]. Though the results of these trials are promising, it is likely that a combination of these agents might provide the optimal treatment to reduce the burden of infection.

Source control

Once it is evident that an infection is present, clarity must be sought on the location and severity. Emergent source control within 12 h should be advocated where feasible. Drainage of any obstruction of the urinary tract and removal of foreign bodies e.g. stones should aid resolution of symptoms and recovery. Of fundamental importance, is local access to theatre facilities to allow timely implementation of source control measures where appropriate. As local departments we have personal duty to insure that this category of emergency case is prioritised.

Adjunctive therapies

Careful management of fluid and electrolyte balance is of utmost importance in the care of the septic patient. Early

goal directed therapy has proven to be of benefit in reducing rates of mortality [23]. Use of volume expanders and vasopressors to maintain adequate oxygen delivery to tissues is essential. Early involvement and close liaison with critical care teams is imperative as these patients are quite unwell, often requiring specialist adjunctive measures which are only provided on the unit.

Conclusion

Sepsis remains a leading cause of morbidity and mortality among urology patients. Where the incidence of HAUTI has generally remained stable in recent times, the incidence of urosepsis in our patients has risen. A multi-faceted approach must be adopted to tackle this problem more effectively. The first steps must be undertaken in advance of any intervention. Both healthcare providers and patients must be extensively educated as to the causes, signs and potential consequences of sepsis. Education must be personalised and environment specific to effectively impact levels of awareness. A structured approach to patient and procedural selection must be adopted to minimise where possible, exposure of vulnerable patients to septic complications. Means by which we monitor for and identify patients with infection must be optimised in line with best available evidence. Once evident, sepsis management must be carried out in conjunction with other specialties including microbiology and critical care to insure timely and effective intervention.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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