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EDITORIAL COMMENTARY

For Whom the bugs *toll*: do uTLR4 levels have a role in screening for urinary tract infection?

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The diagnosis and management of urinary tract infection (UTI) in young children continues to stimulate discussion and research. And rightly so! UTI is not only an important cause of bacterial infection in children, which may be associated with renal tract abnormalities and is a risk factor for renal scarring and hypertension, but also because of the morbidity associated with the infection. It is thus imperative to not only make a correct diagnosis both to initiate appropriate and timely treatment, plus further investigation where indicated, but to also avoid unnecessary treatment and investigation.

Easier said than done! Obtaining a clean mid-stream urine (MSU) from an infant or toddler for culture and sensitivity is challenging. Furthermore, it may take up to 48 h for a result whilst the clinical situation may require immediate commencement of treatment.

Therefore, in clinical practice, rapid 'bedside' screening or 'rapid near patient testing' has been adopted, which may give an indication as to the presence, or not, of a UTI and the need to obtain a 'clean' specimen for microbiological culture and commence treatment. Currently, urinalysis with a dipstick looking for the presence of leukocytes (LE) and nitrites is common practice, and when taken in combination, these have a sensitivity and specificity greater than 90%. These have some limitations in that young infants who frequently empty their bladders may have very few leukocytes present, and nitrites depend on the presence of Gram-negative bacteria and nitrates in the diet. Some laboratories also perform urine microscopy on unspun urine, looking for leukocytes and bacteria, which alone has less accuracy, but in combination with LE and nitrites has improved predictability [1].

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An alternative approach to screening for UTI is to examine the innate immune response and to ascertain whether measurement of biomarkers can discern the presence of a UTI. These biomarkers produced by the immune system include HSP-70 (heat shock protein-70), IL (interleukin), NGAL (neutrophil gelatinase-associated lipocalin and TLRs (toll-like receptors).

HSP-70 is one of a family of proteins produced by cells in response to exposure to stressful conditions, including infection, and is important in proper folding and the maintenance of structure of proteins involved in pro-inflammatory signalling pathways and antigen presentation. They also have a role in the upregulation of TLRs. HSP-70 was studied in the first part of the UTILISE (urinary tract infection and levels of heat shock protein) study, previously published in this journal in which HSP-70 was shown to possibly have some benefit as a screening tool for UTI [2].

In this issue of *Pediatric Nephrology*, Aksu et al. [3] studied TLR4 receptors as biomarkers for predicting UTI and distinguishing between pyelonephritis and cystitis. TLRs — or toll-like receptors — so called after the German word *toll* for 'amazing', and discovered in 1997, have assumed a central role in host immunity. They work by recognising molecular patterns on germs, either anchored on their surfaces or secreted from their insides. These microbiological patterns (Pattern Recognition Hypothesis) are picked up by TLRs widely distributed in mammalian tissues, including bladder and kidney epithelial cells and trigger an alert to the adaptive immune system (T and B cells): i.e. they function as both a sensor (a molecular scout for microbes) as well as a signaller to the adaptive immune system via activation of cytokines and protein kinase C and interleukins. TLRs exist in soluble forms; their expression increases as a response to infection and can be measured in serum and urine (sTLR4).

This is a well-designed study, a continuation of the UTILISE study, involving 37 mainly Turkish centres recruiting 802 children and Aksu et al. are to be complimented on

conducting such a large study and ensuring uniformity in protocols and assessment.

However, the bottom line is that although both uTLR4 and uHSP70 have comparable sensitivity and specificity to leukocyte esterase and nitrites, they are not significantly better, and indeed when used in combination, whilst the specificity increased (97%), the sensitivity decreased; a finding the authors do not explain. The one possible benefit is that uTLR4s are able to distinguish pyelonephritis from cystitis (1.88 ng/ml vs. 1.47 ng/ml); using a cut-off of 1.69 ng/ml, the sensitivity and specificity were 63 and 61%. However, as the authors admit, pyelonephritis is really a clinical diagnosis and albeit in infants the distinction from cystitis is not always easy; this is really academic as in practice any febrile infant with a proven UTI would receive a full course of intravenous antibiotics. Serial uTLR4 was also shown to be of benefit in monitoring response to treatment, but the same is true of C-reactive protein (CRP). Given this, the clinical utility of uTLR4 screening remains unclear.

However, the main benefit of this study is, as the authors comment in their discussion, to stimulate interest in the immune response to infection, especially UTI and to further examine the effectiveness and workings of other biomarkers such as NGAL and LBP (lipospolysaccharide binding protein). The data bank from the UTILISE study is a valuable resource in this regard for further study.

Declarations

Conflict of interest The author declares no competing interests.

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