

## **Abstract**

Lower urinary tract infections account for over 224,000 hospital admissions each year and nearly all of these admissions have the pathophysiological possibility to develop into pyelonephritis; known clinically as an upper urinary tract infection. Acute pyelonephritis, is characterised by inflammation of the renal parenchyma caused by bacteriuria ascending from the bladder, up the ureters to the kidneys. Effective history taking combined with refined physical examination skills are the two most powerful tools to differentiate upper and lower urinary tract infections as well as assisting the practitioner to exclude other differential diagnoses. Utilisation of these skills by the practitioner, together with the recognised presenting symptom triad of flank pain, fever and nausea in this case study, enabled the diagnosis of acute pyelonephritis to be given.

## **Key Words:**

**Pyelonephritis; upper urinary tract infection; lower urinary tract infection; diagnosis; communication; education**

## **Introduction**

This case study will comprehensively explore the aetiology, epidemiology, pathophysiology, clinical assessment of manifestations and diagnosis of acute pyelonephritis via a critical analysis of current evidence. Effective history taking combined with refined physical examination skills are the two most powerful tools to exclude differential diagnoses (Colgan, Williams and Johnson, 2011). Utilisation of these skills by the practitioner, together with the recognised presenting symptom triad of flank pain, fever and nausea (British Medical Journal, 2018), enabled the diagnosis of acute pyelonephritis to be given. To respect confidentiality and ensure anonymity, the synonym 'patient' will be used throughout (NMC 2018; Health and Care Professions Council, 2016).

## **Definition, aetiology and epidemiology**

Acute pyelonephritis, known clinically as an upper urinary tract infection (UTI), is defined as a tubulointerstitial disorder characterised by inflammation of the renal parenchyma caused by bacteriuria ascending from the bladder up the ureters to the kidneys (Choong, Antypas and Richter-Dahlfors, 2015). Bethel (2012) estimated that annually, 1 in every 830 people in England develop pyelonephritis. However, the exact epidemiology and economic cost

remains unknown due to the overlap of treatment in primary and secondary care (Bethel, 2012). In comparison, a lower UTI has an annual incidence of 3 in every 100 people which accounts for over 224,000 hospital admissions each year (National Institute for Health and Care Excellence (NICE), 2014) with an associated £316 million health-care cost (McDonald *et al.*, 2014). It is important to emphasise that nearly all of these admissions have the pathophysiological possibility to develop into pyelonephritis if treatment is delayed or inadequate.

The patient presented with numerous pyelonephritis risk factors (see Table 1) which are comprehensively explored in research. Pyelonephritis resulting in admission to secondary care is nearly five times more likely in females than males, with 11.7 versus 2.4 admissions per 10,000 cases respectively (Ramakrishnan and Scheid, 2005). Various reasons to justify this gender disparity are explored, with Bethel (2012) confirming the primary reason being variation in anatomy. The turbulence pressure generated in the female urethra allows backflow of bacteria into the bladder during micturition (Franz and Horl, 1999). Moreover, in females, a shorter urethra combined with the closer proximity of the urethral orifice to the anal region facilitates bacteria reaching the kidneys and increases susceptibility to pyelonephritis (Bethel, 2012). This is verified by the aetiology of pyelonephritis as in over 80% of female cases, the causative agent is bacteria derived from the hosts own bowel flora, namely *Escherichia Coli*, as in this case (Springall, Sheerin and Sacks, 2002). Other organisms include *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Proteus mirabilis* (Neumann and Moor, 2014).

Matuszkiewicz-Rowińska, Małyszko and Wieliczko (2015) illustrated that hormonal changes during the menstrual cycle increase the risk of pyelonephritis by reducing ureteral peristalsis, aiding the rapid colonisation of bacteria. A frequently cited journal by Franz and Horl (1999) interestingly explained how oestrogen and the use of many oral contraceptives increases the risk. Oestrogen changes the quantity and quality of the mucopolysaccharide layer lining the bladder and urethra which reduces the visceral smooth muscle tone and contractility, increasing the probability of bacterial attachment to the tubular-epithelium (Franz and Horl, 1999). Regular sexual activity, another risk factor highlighted in this case, alters the normal lactobacillus-dominant vaginal flora and promotes invasion of *Escherichia Coli* bacteria into the vagina which acts as a bacterial reservoir. (Scholes *et al.*, 2005). Anatomical disparities, hormonal changes and regular sexual activity, as seen in Table 1,

pathophysiologically rationalise the increased incidence of pyelonephritis in women aged 18-49 (British Medical Journal, 2018).

### **History of UTI's**

The patient reported a history of lower UTI's, two in the last twelve months, predisposing to pyelonephritis (Scholes *et al.*, 2005). A growing quantity of evidence implicates genetic pathophysiological variations in patients with recurrent UTI's (Ambite *et al.*, 2016). Ambite *et al.* (2016) highlighted differences that negatively affect the hosts immune response which included altered recognition of receptor molecules, reduced cytokine release and decreased neutrophil activation, all of which lead to increased amounts of renal scarring. Renal scarring, a complication of pyelonephritis, causes dilation of the kidney tubules and changes the glomerular-capillary pressure, reducing the efficiency of the normal filtration role of the kidneys and predisposes to recurrence of the condition (Choong, Antypas and Richter-Dahlfors, 2015). Renal scarring can further contribute to the development of acute renal failure and renal hypertension (Bethel, 2012).

### **Antibiotic prescribing**

Linking pathophysiology with clinical guidelines, repeated and prolonged courses of antibiotics increases susceptibility to pyelonephritis due to the increased resistance profile of microorganisms to antibiotic treatment as their virulence genes are strengthened (Raeispour and Ranjibar, 2018). In *Escherichia Coli*, *Haemolysin A* is released which causes cellular tissue damage and dysfunction of the immune response (Raeispour and Ranjibar, 2018). Additionally, *P-fimbriae* facilitates bacteria attachment specifically to the epithelium receptors in the urogenital tract (Franz and Horl, 1999). As a result, national and local guidelines recommend limiting antimicrobial prescribing to a seven-day course (NICE, 2018).

### **Diagnosis and Complications of Pyelonephritis**

The mortality rate for acute pyelonephritis has significantly reduced over the last three decades and is attributable to revised clinical guidelines. It has decreased from an estimated near 10% in 1990 (Robert, Geere and Coldman, 1991) to 0.7%-1.65% in 2017 (British Medical Journal, 2018) but the complications of pyelonephritis, as discussed, remain unchanged. However, these complications can be significantly reduced with early diagnosis through clear history taking of the presentation (British Medical Journal, 2018).

History taking, although an acquired clinical skill, is dependent on the patient's cognitive and sensory ability to express their symptoms and the severity of the condition (Bethel, 2012). Norouzinia *et al.* (2016) concluded that pain, discomfort and anxiety, as were noticeably present in this case, can negatively affect communication and a patient's ability to convey information accurately. Therefore, prior to history taking, these elements were addressed by ensuring adequate analgesia and a discussion with the practitioner to prevent a delayed or incorrect diagnosis.

Diagnosis for pyelonephritis can be challenging as the presentation of fever and nausea, considered two of the triad of predominant markers for pyelonephritis, are not specific to the condition (Bethel, 2012). Furthermore, the onset of symptoms can vary from hours to several days with the severity of symptoms substantially fluctuating between patients (British Medical Journal, 2018). Colgan, Williams and Johnson (2011) stress that flank pain, conspicuous in this case, is universal in patients with pyelonephritis, but the key abnormal examination finding is tenderness on palpation of the costovertebral angle. Due to the anatomical position of the kidneys, palpation of the patient's right costovertebral angle elicited renal tenderness which strongly suggested an inflammatory process in the patient's right kidney (Faust and Tsung, 2017). Importantly, nephrolithiasis and ureterolithiasis, which also present with flank pain, do not typically present with tenderness of the costovertebral angle (Colgan, Williams and Johnson, 2011). This allowed these differentials to be excluded upon examination.

## **Pain**

The patient presented with acute flank pain due to the activation of nociceptors on a cellular level (Pham *et al.*, 2017). Nociceptors are stimulated by inflammatory mediators, specifically prostaglandins and cytokines, which are released by the kidney in response to cellular damage (Pham *et al.*, 2017). Nociceptors are also stimulated in pyelonephritis by the smooth muscle distention of the renal capsule caused by the vascular leakage as part of the inflammatory process (Choong, Antypas and Richter-Dahlfors, 2015). Current research has suggested a protective role of Toll-Like Receptor (TLR) 4, the key receptor to *Escherichia Coli* bacteria, as a mediator of pyelonephritis-associated pain responses that are independent of inflammation (Rosen and Klumpp, 2014). However, the mechanism remains unclear (Rosen and Klumpp, 2014). Once activated, the visceral afferent fibres synapse in the dorsal horn of the spinal cord and ascend via the lateral spinothalamic tract

to the somatosensory area in the brain for localisation and conscious recognition of pain by the patient (Martini and Nath, 2009). Adding to the complexity of diagnosis, although not seen in this case, patients with pyelonephritis can present with referred visceral pain to the groin due to the convergence of different afferents on the same dorsal horn neurones in the spinal cord (Martini and Nath, 2009). Nausea and vomiting are associated symptoms of pain, as seen in this case.

### **Pyrexia**

The patient presented with pyrexia and associated rigors. The generation of a fever occurs when the lipopolysaccharides of the bacteria stimulate the production of prostaglandin (PGE<sub>2</sub>), which acts in the organum vasculosum of the lamina terminalis (OVLT) in the hypothalamus (Walter *et al.*, 2016). The increased synthesis of PGE<sub>2</sub> slows the firing rate of the warm sensitive neurones resulting in an elevated body temperature. Walter *et al.* (2016) highlight that the maintenance of a fever is caused by cytokines produced during immune response which directly stimulate the OVLT. In addition to rigors, the patient presented as hypotensive and tachycardic. This is common in the acute phase of pyrexia due to the combination of redistributed blood flow, nitric oxide-induced vasodilation and hyperdynamic circulation (Walter *et al.*, 2016).

Walter *et al.* (2016) confirm that pyrexia has three key benefits. An elevated body temperature inhibits bacterial replication as this occurs optimally at temperatures below 37°C (Walter *et al.*, 2016). Additionally, pyrexia increases the efficacy of antimicrobials and enhances the hosts immune response (Walter *et al.*, 2016). However, pyrexia has a negative effect on kidney function. A morphological study by Vlad *et al.* (2010) confirm glomerular capillary dilation, interstitial haemorrhage, small vessel vascular stasis and reduced renal blood flow occur with pyrexia, increasing the plasma creatinine and urea concentrations and reducing the glomerular filtration rate.

Treating pyrexia is controversial in literature due to the discussed benefits being inhibited by prescribing medication (Walter *et al.*, 2016). However, this is not recognised in practise as pyrexia is always treated. In this case, Paracetamol was prescribed as recommended in the NICE guidelines (2017) due to its effectiveness at treating pyrexia and rigors.

Furthermore, non-steroidal anti-inflammatory medications are not recommended due to their nephrotoxicity which can cause further renal impairment (British National Formulary, 2018). Ultimately, patient comfort is the foremost priority.

## **Importance of urinalysis**

Clinical guidelines recommend urinary dipstick tests to differentially diagnose acute pyelonephritis from those with similar symptoms (NICE, 2017). The patient had a positive urine dipstick analysis for nitrites which is a rapid screening test and surrogate marker of bacteraemia (Douglas, Nicol and Robertson, 2013). Nitrites are not normally found in urine but various bacteria, including *Escherichia Coli*, convert urinary nitrates to nitrites by the enzyme reductase in response to nitrosative stress, which facilitates the organism's further colonisation (Majid and Buba, 2010). Importantly, the nitrate dipstick was taken from a closed container by the practitioner as the dipstick reagent is susceptible to aerial oxidation which can produce a false-positive result (Simerville, Maxted and Pahira, 2005). Therefore, the presence of nitrites confirmed bacteriuria in the patient.

Before interpreting the urine dipstick results, the practitioner measured the specific gravity of the sample, as this is directly proportional to urine osmolarity and can support false-negative or false-positive results (Kumar and Clark, 2017). Moreover, Franz and Horl (1999) highlight that not all uropathogens are nitrate-reducing organisms, which means false-negative results can occur. For this reason, nitrite dipstick results should never be used in isolation to exclude bacteriuria. Owing to the low sensitivity of the nitrite test across all organisms, a urinary culture analysis was also performed as this is recognised as the gold standard in the national guideline (NICE, 2018).

Additionally, the patient urine dipstick was positive for leucocytes, correlating to the presence of pyuria (British Medical Journal, 2018). The dipstick result confirmed the presence of leucocyte esterase which is an endoleukocyte enzyme released upon lysis of white blood cells (Hooton, 2012). Leucocytes are the predominant inflammatory cell in the immune response to bacterial pyelonephritis (Lager and Abrahams, 2013).

The cell walls of bacteria, specifically *Escherichia Coli*, contain lipopolysaccharides which are detected by TLR4, TLR5 and TLR11 found on the apices of the distal tubules (Choong, Antypas and Richter-Dahlfors, 2015). TLR4 signalling induces the production of cytokines, namely IL-6, IL-1 and tumour necrosis factor, which co-ordinate the cascading immune and inflammatory response. Neutrophils, a specific type of leucocyte, move down this chemotaxis gradient to the infection site and clear the bacteria via phagocytosis (Springall, Sheerin and Sacks, 2002). The patient's blood results illustrated this pathophysiological process as the C-Reactive Protein (CRP) was raised at over 100. CRP is an infection

biomarker synthesized by the liver in response to IL-6 and, along with the positive urine culture, justified the use of antibiotics in this case (Simon *et al.*, 2004). Simon *et al.* (2004) emphasise the clinical limitation of interpreting a CRP result in isolation as it is unable to differentiate between a bacterial and noninfective cause of systemic inflammation.

This significant neutrophil recruitment causes the release of proteolytic enzymes which alter the physiology of the infected kidney by increasing vascular permeability and breaking down the epithelium (Choong, Antypas and Richter-Dahlfors, 2015). As a result, the endoleukocyte enzymes leak into the urine (Choong, Antypas and Richter-Dahlfors, 2015). Lager and Abrahams (2013) equally confirm the significant presence of neutrophils in pyelonephritis by histological diagnostic features. These include pathognomonic pus cell casts found within the tubule lumens in a neutrophil-predominant inflammatory infiltrate (Lager and Abrahams, 2013). This was illustrated by a raised white blood cell count, namely neutrophil count, in the patient's blood results.

As the patient was female, it was ruminated if this was a true positive result as leucocytes can originate from sites of inflammation in the genital tract as well as the kidneys (Franz and Horl, 1999). Furthermore, research clarifies that leukocyturia can continue even after bacteriuria has symptomatically resolved (Franz and Horl, 1999). This could have been explained in this case by the patient's recent lower UTI. On the contrary, the positive leucocyte test, combined with the patient's examination and blood results, strengthened the diagnosis of pyelonephritis.

The patient's urine dipstick also indicated proteinuria. The pathophysiological phenomenon of proteinuria in cases of pyelonephritis without pre-existing renal disease has been extensively researched but with incongruent conclusions. A quantitative study by Mokham *et al.* (2014) concluded that the prevalence of proteinuria in pyelonephritis is 90.9%-98.7% with variances due to the proximal or distal tubular leakage of proteins. Proximal tubular involvement causes a higher leakage level of tubular proteins and amino acids because of the increased effects of the inflammatory process (Mokham *et al.* 2014). Conversely, Carter *et al.* (2006) established in a systematic review that positive protein tests occur because of the reaction of the test pad with leucocytes and bacterial proteins. It was also concluded to be a result of alkalinisation of the urine caused by the bacterial breakdown of urea, rather than due to the tubular leakage of proteins. Further research is required in this area, particularly utilising immunoassay methods as these methods are not susceptible to the

highlighted problems of urine test strips (Carter *et al.*, 2006). However, on reflection, for these methods to be implemented routinely, the contemporary economical barrier must first be overcome. Despite the exact nature of proteinuria being undetermined, proteinuria is a recognised feature of pyelonephritis.

The cellular structure of the nephron increases its sensitivity to infection. Choong, Antypas and Richter-Dahlfors (2015) highlight that the nephron contains different types of epithelia, with thin squamous cell epithelia lining the glomerular capsule in the renal corpuscle being specific for filtration, whereas cuboidal cell epithelia lines the tubular system is specific for reabsorption. This variation in the epithelial structure and function throughout the different segments, combined with the changing chemical composition of the urine, has increased the colonising ability of bacteria. (Choong, Antypas and Richter-Dahlfors, 2015).

In this patient, gram-negative rods of *Escherichia Coli* were isolated during microbiological analysis of the patient's urine culture. *Escherichia Coli* has numerous virulence factors which enabled its rapid colonisation in the kidneys in this case (Raeispour and Ranjibar, 2018). Examples of these factors are *Haemolysin A* and *P-fimbriae* as previously discussed, but others include the syntheses of *Aerobactin* and *Enterobactin* which are iron binding proteins required for bacterial replication (Franz and Horl, 1999). *P-fimbriae* is crucial for mediating the binding to the epithelium in the early stages of colonisation, whereas *Type 1 fimbriae* is essential for colonisation across the luminal centre of the tubule where there is no epithelium and significant hydrodynamic forces are identified from the filtrate (Choong, Antypas and Richter-Dahlfors, 2015). *Type 1 fimbriae* has adapted to be capable of inter-bacterial binding which occurs via a catch-bond mechanism, allowing the bacteria to bind and remain in the microenvironment rather than being washed out of the system.

From a clinical perspective, the infection-associated inflammatory response has an impact on normal renal function. Choong, Antypas and Richter-Dahlfors (2015) express that bacterial colonisation causes sloughing of the tissue, clot formation, localised ischaemia and cellular blebbing as immune-inflammatory defence mechanisms are triggered to protect the patient from bacterial dissemination and systemic spread. These cause a degree of tubular obstruction and lead to changes in the hydrostatic pressure, negatively impacting the glomerular filtration rate and seen in patient's blood results.

Kumar and Clark (2017) elucidate that hydronephrosis from obstruction, either by renal calculi, cysts, malignant tumours or infected collections, gives a causative reason for a patient's pyelonephritis. Consequently, in all patients, these differential diagnoses need to be excluded by carrying out an ultrasound of the kidneys and bladder, as completed in this case. Ultrasound is the imaging method of choice for renal diagnosis as it has two main advantages of avoiding both ionising radiation and the nephrotoxic intravascular contrast medium utilised in computerised tomography scans (Kumar and Clark, 2017). The patient's ultrasound confirmed no obstruction, strengthening the theory of bacteraemia being the solitary cause of pyelonephritis.

### **Patient Education**

Patient education and the promotion of self-management have been identified as crucial treatment elements to reduce the risk of recurrence and promote health behaviours (Hooton, 2012). Health promotion information, endorsed by Kumar and Clark (2017), was provided by the practitioner and included recommendations such as discouraging the use of soaps, voiding post sexual intercourse, avoiding tight fitting underwear and not delaying urination. However, a case-control study by Hooton (2012) revealed that these have no statistical significance in reducing the recurrence of pyelonephritis. Furthermore, increased fluid intake and drinking cranberry juice were recommended by the practitioner, both of which are supported by a Cochrane review which described these as biological mediators, inhibiting uropathogens adhesions to uroepithelial cells (Jepson and Craig, 2008). On the contrary, a more recent randomised placebo-control trial concluded that there is no benefit in drinking cranberry juice or increasing fluid intake on the recurrence of pyelonephritis (Barbose-Cesnik *et al.*, 2011). Despite inconclusive clinical research, recommending health behaviours and biological mediators remain an affirmed part of clinical practise in pyelonephritis management as they pose a low risk to patients.

### **Communication**

Cole and Bird (2013) highlight the importance of patient engagement through both clear communication during history taking and by promoting collaborative management in excluding differential diagnoses effectively. On analysis and clinical reflection by the practitioner, effective communication was facilitated during the patient's stay by clearly explaining the diagnosis and treatment and by addressing any concerns arising due to the psychological effects of the diagnosis.

Verbal and written communication with the multidisciplinary team is crucial in pyelonephritis management to optimise treatment (British Medical Journal, 2018). In this case, discussions with the microbiologists and pharmacists were necessary to ensure effective antimicrobial prescription in line with antimicrobial stewardship (NICE, 2014). The patient discharge letter was comprehensively written and included safety netting recommendations for the patient's general practitioner in the instance of recurrence. An outpatient appointment with a renal consultant was also arranged to ensure there were no residual effects on the patient's renal function.

### **Conclusion**

It is evident that to diagnose pyelonephritis correctly, comprehensive understanding of its pathophysiology is required, including the critical analysis of research. Clinically, effective history taking and the identification of risk factors can support the complexity of pathophysiology, aiding the main objective of successful patient care.

## References

- Ambite, I., Rydstrom, G., Schwaderer, A. and Hains, D. (2016) 'The Genetics of Urinary Tract Infections and the Innate Defence of the Kidney and Urinary tract', ***Journal of Paediatrics Genetics***, 5(1), pp. 25–32. doi: 10.1055/s-0035-1557110.
- Barbosa-Cesnik, C., Brown, M.B., Buxton, M., Zhang, L., DeBusscher, J. and Foxman, B. (2011) 'Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial', ***Clinical Infectious Diseases***, 52(1), pp. 23-30. doi: 10.1093/cid/ciq073.
- Bethel, J. (2012) 'Acute Pyelonephritis: risk factors, diagnosis and treatment', ***Nursing Standard***, 27(5), pp. 51-56. doi: 10.7748/ns2012.10.27.5.51.c9334.
- British Medical Journal (2018) ***Best Practise Acute Pyelonephritis***. Available at: <https://bestpractice.bmj.com/topics/en-gb/551> (Accessed: 30 November 2018).
- British National Formulary (2018) ***Ibuprofen***. Available at: <https://bnf.nice.org.uk/drug/ibuprofen.html> (Accessed: 1 December 2018).
- Carter, J.L., Tomson, C.R.V., Stevens, P.E. and Lamb, S.E.J. (2006) 'Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review', ***Nephrology Dialysis Transplantation***, 21(11), pp. 3031-3037. doi: 10.1093/ndt/gfl373.
- Choong, F.X., Antypas, H. and Richter-Dahlfors, A. (2015) 'Integrated Pathophysiology of Pyelonephritis', ***Microbiology Spectrum***, 3(5), pp. 1-15. doi: 10.1128/microbiolspec.UTI-0014-2012.
- Cole, S. and Bird, J. (2013) ***The Medical Interview: The Three-Function Approach***. Philadelphia: Saunders. Third edition.
- Colgan, R., Williams, M. and Johnson J.R. (2011) 'Diagnosis and Treatment of Acute Pyelonephritis in Women', ***American Family Physicians***, 84(5), pp. 519-526. Available at: <https://www.aafp.org/afp/2011/0901/p519.html> (Accessed: 30 November 2018).
- Douglas, G., Nicol, F. and Robertson, C. (2013) ***Macloads Clinical Examination***. London: Churchill Livingstone. Thirteenth edition.

Faust, J.S. and Tsung, J.W. (2017) 'Eliciting renal tenderness by sono-palpation in diagnosing acute pyelonephritis', **Critical Ultrasound Journal**, 9(1), pp. 1-4. doi: 10.1186/s13089-016-0056-6.

Franz, M. and Horl, W.H. (1999) 'Common errors in diagnosis and management of Urinary Tract Infections: pathophysiology and diagnostic technique', **Nephrology Dialysis Transplantation**, 14(11), pp. 2746-2753. Available at: <https://academic.oup.com/ndt/article/14/11/2746/1807919> (Accessed: 16 November 2018).

Health and Care Professions Council (2016) **Standards of Conduct, Performance and Ethics**. Available at: <http://www.hcpc-uk.org/publications/standards> (Accessed: 30 November 2018).

Hooton, T.M. (2012) 'Uncomplicated Urinary Tract Infections', **The New England Journal of Medicine**, 366(11), pp. 1028-1037. doi: 10.1056/NEJMcp1104429.

Jepson, R.G. and Craig, J.C. 'Cranberries for Preventing Urinary Tract Infections', **Cochrane Database of Systematic Reviews**, 23(1), pp. 1-80. doi: 10.1002/14651858.CD001321.pub4.

Kumar, P. and Clark, M. (2017) **Kumar & Clark's Clinical Medicine**. Edinburgh: Elsevier. Ninth edition.

Lager, D.A. and Abrahams, N.A. (2013) **Practical Renal Physiology: A Diagnostic Approach**. Philadelphia: Elsevier Saunders.

Majid, A.L and Buba, F. (2010) 'The Predictive and Discriminant Values of Urine Nitrites in Urinary Tract Infection', **Biomedical Research**, 21(3), pp. 297-299. Available at: <http://www.alliedacademies.org/articles/the-predictive-and-discriminant-values-of-urine-nitrites-in-urinary-tract-infection.html> (Accessed: 16 November 2018).

Martini, F.H. and Nath, J.L. (2009) **Fundamentals of Anatomy and Physiology**. San Francisco: Pearsons Education. Eighth edition.

Matuszkiewicz-Rowińska, J., Małyшко, J. and Wieliczko, M. (2015) 'Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems', **Archives of Medical Science**, 11(1), pp. 67-77. doi: 10.5114/aoms.2013.39202.

McDonald, H.I., Nitsch, D., Millett, E.R.C., Sinclair, A. and Thomas, S.L. (2014) 'New estimates of the burden of acute community- acquired infections among older people with

diabetes mellitus: a retrospective cohort study using linked electronic health records', *Diabetic Medicine*, 31(5), pp.606-614. doi: 10.1111/dme.12384.

Mohkam, M., Shabestani, G., Kompani, K., Esfandiar, N., Sharifian, M., Gorji, F.A. and Dalirani, R. (2014) 'Frequency of Massive Proteinuria in Childhood Pyelonephritis and the Response to Antibiotic Therapy', *Journal of Paediatric Nephrology*, 1(3), pp. 121-124.

National Institute for Health and Care Excellence (2014) **Antimicrobial Stewardship: system and process for effective microbial medicine use**. Available at: <https://www.nice.org.uk/guidance/ng15> (Accessed: 16 November 2018).

National Institute for Health and Care Excellence (2014) **Quality Standards and Indicators: Briefing paper**. Available at: <https://www.nice.org.uk/guidance/qs90/documents/urinary-tract-infection-in-adults-qs-briefing-paper2> (Accessed: 10 November 2018).

National Institute for Health and Care Excellence (2017) **Clinical Knowledge Summaries: Pyelonephritis-acute**. Available at: <https://cks.nice.org.uk/pyelonephritis-acute> (Accessed: 18 November 2018).

National Institute for Health and Care Excellence (2018) **Pyelonephritis (acute): antimicrobial prescribing**. Available at: <https://www.nice.org.uk/guidance/ng111> (Accessed: 4 November 2018).

Neumann, I. and Moore, P. (2014) 'Pyelonephritis (acute) in non-pregnant women', *BMJ Clinical Evidence*, 11(1), pp. 807-814. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220693> (Accessed: 18 November 2018).

Norouzinia, R., Aghabarari, M., Shiri, M., Karimi, M. and Samami, E. (2016) 'Communication Barriers Perceived by Nurses and Patients', *Global Journal of Health Science*, 8(6), pp. 65-74. doi: 10.5539/gjhs.v8n6p65.

Pham, P.C., Khaing, K., Sievers, T.M., Pham, P.C., Miller, J.M., Pham, S.V., Pham, P.A. and Pham, P.T. (2017) 'Update on pain management in patients with chronic kidney disease', *Clinical Kidney Journal*, 10(5), pp. 688–697. doi: 10.1093/ckj/sfx080.

Raeispour, M. and Ranjbar, R. (2018) 'Antibiotic resistance, virulence factors and genotyping of Uropathogenic *Escherichia coli* strains', *Antimicrobial Resistance and Infection Control*, 7(118), pp. 1-9. doi: 10.1186/s13756-018-0411-4.

- Ramakrishnan, K. and Scheid, D.C. (2005) 'Diagnosis and Management of Acute Pyelonephritis in Adults', ***American Family Physicians***, 71(5), pp. 932-942.
- Robert, F.J., Geere, I.W. and Coldman, A. (1991) 'A three-year study of positive blood cultures, with emphasis on prognosis', ***Review of Infectious Diseases***, 13(1), pp. 34-46.
- Rosen, J.M. and Klumpp, D.J. (2014) 'Mechanisms of Pain from Urinary Tract Infection', ***International Journal of Urology***, 21(1), pp. 26–32. doi: 10.1111/iju.12309.
- Scholes, D., Hooton, T.M., Roberts, P.L., Gupta, K., Stapleton, A.E. and Stamm, W.E. (2005) 'Risk factors associated with acute pyelonephritis in healthy women', ***Annals of Internal Medicine***, 142(1), pp. 20-27.
- Simerville, J.A., Maxted, W.C. and Pahira, J.L. (2005) 'Urinalysis: A Comprehensive Review', ***American Family Physicians***, 71(6), pp. 1153-1162.
- Simon, L., Gauvin, F., Amre, D.R., Saint-Louis, P. and Lacroix, J. (2004) 'Serum Procalcitonin and C-Reactive Protein Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis', ***Clinical Infectious Diseases***, 39(2), pp. 206–217. doi: 10.1086/421997.
- Springnall, T., Sheerin, N.S. and Sacks, S.H. (2002) Breaching host defences in the urinary tract', ***Hong Kong Journal of Nephrology***, 4(1), pp.13-21.
- Vlad, M., Lonescu, N., Ispas, A.T., Giuvărășteanu, I., Ungureanu, E. and Stoica, C. (2010) 'Morphological changes during acute experimental short-term hyperthermia', ***Journal of Morphology and Embryology***, 51(4), pp. 739–744.
- Walter, E.J., Hanna-Jumma, S., Carraretto, M and Forni, L. (2016) 'The pathophysiological basis and consequences of fever', ***Critical Care***, 20(200), pp. 1-10. doi: 10.1186/s13054-016-1375-5.