Editorial

Dr. Lawrie Bott MB, BS(Hons), FRCPA
CEO

Welcome to the Summer edition of the Doctors’ Newsletter. As the new CEO of Hobart Pathology I am delighted to introduce this newsletter.

For those of you whom I have not yet met, I am a general Pathologist who has worked in both community and hospital environments. I have worked in most pathology disciplines throughout my career, in addition to my administrative role, I now predominantly work in the clinical pathology area.

I am delighted to have moved to Tasmania to work as a Pathologist. Hobart Pathology is one of the most highly regarded pathology practices in Australia and I am pleased to be part of the organisation. I appreciate the welcome I have received from everyone and look forward to working with you.

On behalf of all the staff of Hobart Pathology, I would like to thank you for your ongoing support. We greatly value it and, in turn, it assists us in our commitment to provide you with state of the art diagnostic pathology.

Dr. Daniel Owens FRACP FRCPA
Medical Director

This edition of the Doctors’ Newsletter focuses on urine pathology.

We have included a diverse range of articles covering urine microbiology, urine cytology and the investigation of polyuria.

I hope that you find this information of use in your clinical practice.
Laboratory Diagnosis of Urinary Tract Infection:
Specimen collection and transport

Appropriate specimens for examination are mid-stream or "clean-catch" urine, or a specimen collected at catheterisation or suprapubic aspiration. Collections into a sterile container should be transported to the laboratory for processing as soon as possible.

If the specimen cannot be examined within 30 minutes of collection it should be stored at 4 degrees until it can be despatched to the laboratory and it must be cultured within 24 hours of being passed.

Even if correct techniques of collection are used a urine specimen may be contaminated with bacteria from the distal urethra or perineal region.

Urine dipstick testing

Nitrite test – a surrogate marker for bacteruria if organisms which reduce nitrate to nitrite, such as members of the enterobacteriaceae family (for example E. coli), are present. Some significant pathogens however do not reduce nitrate (for example Staphylococcus saprophyticus and Enterococci).

Leucocyte esterase test – an indicator of pyuria with 79–95% sensitivity and 94–98% specificity in detecting >10 leucocytes/μL of urine.

While these tests correlate well with high bacterial count UTI, they miss significant numbers when lower counts are present in acutely symptomatic young women. UTI may be missed in up to 20% of patients if a negative urinalysis is used to rule out UTI.

Urine microscopy

Red blood cells, white blood cells and epithelial cells are examined and quantitated by microscopy of uncentrifuged urine.

RBC $\geq 10 \times 10^6$ erythrocytes/L indicates haematuria which may be of glomerular or non-glomerular origin. Dysmorphic red cells (cells with a variety of sizes, shapes and fragmentation) identified on phase contrast microscopy are indicative of glomerular origin (eg. glomerulonephritis, vasculitis) though adverse storage and transport conditions may induce artefactual changes. In non-glomerular bleeding, red cells are more uniform in size and shape and suggest lower urinary tract origin (eg. infection, bladder neoplasm, calculi).

WBC $\geq 10 \times 10^6$ leucocytes/L (associated with inflammation) is defined as significant pyuria.

Epithelial cells $\geq 10 \times 10^6$ squamous epithelial cells/L indicates skin / mucosal contamination of the sample.

Casts – red cell, white cell, granular and renal tubular casts may be of pathological significance indicating kidney / glomerular disease. Hyaline casts are less specific for renal disease.

Crystals – in urine are not uncommon and are rarely significant. Phosphates, urates and oxalates may occur in normal urine sediment; developing as urine cools.

Urine culture

The benchmark definition of significant bacteruria - established by Kass in 1956 - used a criteria of $\geq 10 \times 10^8$ bacteria/L to distinguish significant bacteruria from that associated with contamination. Using this criteria there was a positive predictive value of 98%. Subsequent studies, however showed a negative predictive value of 65%, especially in the sub-population of young symptomatic women. In this group and in some other situations (such as suprapubic aspirates) the threshold for significant bacteruria has been lowered to $10^5$ bacteria/L (with 95% sensitivity and 85% specificity).

Interpretation of results

The interpretation of urine microscopy and culture results by level of bacteruria is dependent on clinical history, age and sex of the patient and co-morbidities.

Asymptomatic bacteruria

The presence of significant numbers of bacteria in the urine in the absence of symptoms of UTI are reported in 1-5% of healthy pre-menopausal women, 25-50% of male and female nursing home residents (up to 30% of whom may develop a symptomatic UTI within 6 months) and up to 100% of patients with a long-term indwelling catheter. Only in some settings is there evidence of benefit with treatment of asymptomatic bacteruria. These senarios include:

- during pregnancy there is a 25-30% risk of developing pyelonephritis and adverse pregnancy outcome
- before urological procedures where mucosal bleeding is anticipated (eg.TURP)
- catheterised patients if signs of systemic infection; before urological procedures; other risk factors (eg. neutropaenia, transplantation) present
- elderly patients with with evidence of obstruction, poor bladder emptying, stroke or diabetes mellitus – which may heighten the risk of infection and treatment may be indicated.
Symptomatic bacteruria

Symptoms or signs increasing the pre-test probability of UTI include dysuria, urinary frequency, haematuria, costovertebral angle tenderness, and nitrates and/or leucocyte esterase on urine dipstick.

- 10-20% of women will experience at least one UTI in their lifetime
- 1-2% of infants will experience a UTI – often associated with abnormalities of the urinary tract – and radiological investigations are usually indicated
- 2% of males and 8% of females have experienced a UTI by the age of 10
- elderly males and females with predisposing factors including obstructive uropathy, uterovaginal prolapse, vaginal epithelial atrophy, or soiling due to faecal incontinence have a higher incidence of UTI

Organisms

- >95% of uncomplicated UTIs are caused by a single organism
- 70-95% of uncomplicated UTIs are due to E. coli, 5-10% due to Staphylococcus saprophyticus
- 20-50% of complicated UTIs are due to E. coli. Other common organisms include other gram negative bacteria (eg. Proteus, Klebsiella, Enterobacter, Pseudomonas spp., Enterococci, Group B Streptococcus)
- catheter / instrumentation-related infections are often polymicrobial with more than one species present in significant numbers; which may include resistant strains if patient has had previous repeated courses of antibiotics. Organisms present can include opportunistic pathogens such as Acinetobacter, Stenotrophomonas spp., Corynebacteria spp.

Antibiotic sensitivity testing

In the presence of significant pyuria and bacteruria the laboratory performs and reports the appropriate antibiotic sensitivity tests for the organism(s) isolated. Please refer to page 7 for current data from our laboratory detailing sensitivity patterns of common urine isolates.

Author: Dr John Roberts

References:
1. Munro, R and Chambers, I. Laboratory Diagnosis of Urinary Tract Infection : Common Sense Pathology Unit 5, October 2002.
2. RCPA Manual Version 4 http://www.rcpamanual.edu.au
3. Bell, S. and Outhred. An alternative approach to the Diagnosis of UTI in Adults : Common Sense Pathology, July 2006
Urine Cytology

Urothelial cells are present in all urine specimens and exfoliate readily from tumours of the urothelial lining. Urine cytology is therefore an important primary method of diagnosing urothelial tumours, and in combination with cystoscopy and biopsy, it is used as an adjunct. Less commonly, other tumours such as renal and prostate adenocarcinomas can be diagnosed on urine cytology but this modality is not the primary or most reliable diagnostic method. Cells from these tumours usually are present in urine only when they are significantly advanced.

Cytologic examination of urine is performed primarily in:

1) the diagnostic evaluation of symptomatic patients. The most common presenting symptom in patients with bladder cancer is gross haematuria. Patients with gross or microscopic haematuria must be further evaluated until the source of the bleeding has been securely established. Cytologic examination of the urine is indicated in these cases.

2) the follow-up and monitoring of patients with known and treated disease.

The overall sensitivity of urine cytology for primary detection of bladder cancer, ranges from 47% to 97% in the literature. The specificity ranges from 3% to 5%. It is important to note that the sensitivity significantly improves the higher the grade the tumour is.

The most important consideration when collecting a voided urine specimen for cytology is to avoid cellular degeneration - which renders assessment of the urothelial cells suboptimal. For this reason it is desirable that the first voided urine of the day is discarded and a subsequent voided urine sample is sent for cytology. Processing of the specimen should ideally occur within 4 hours of collection and the sample should be stored at 4-8 degrees celsius prior to transport to the laboratory.

Figure 1: Normal urothelial cells

Figure 2: Atypical urothelial cells showing marked variation in nuclear size and shape; consistent with transitional cell carcinoma

In summary, urine cytology is an established diagnostic procedure in the primary diagnosis and follow-up of patients with urothelial carcinoma and has an acceptable sensitivity and specificity.

Author: Dr Shaun Donovan


Polyuria

Polyuria usually is associated with polydipsia. Polydipsia may occur with dehydration, without resulting polyuria.

Definition:
Excretion of urine in excess of 3 litres per day.

Investigation:
Many people imagine they have polyuria when they don’t, so it is important that a 24 hour urine volume result be assessed before too many other investigations proceed. Diuretics and alcohol (particularly beer) are common causes. If a cause other than diuretics is being sought, diuretics should be ceased if possible, as they may affect the investigations.

Causes:
Some of the more common causes are discussed below but the most common cause in the general population is diabetes mellitus.

Glycosuria
Polyuria is due to the osmotic effect of the glucose in the urine. All patients with glycosuria should be checked for diabetes.
Fasting or postprandial glucose levels are usually elevated in patients with glycosuria but sometimes are not. Some people have a low renal threshold for excretion of glucose and may have normal plasma glucose levels. (Normal renal threshold is about 10mmol/L.) If this is the case, a urine dipstick will show glucose.

**Hypercalcaemia**

Hypercalcaemia causes polyuria and several mechanisms may be involved. Primary hyperparathyroidism is not uncommon in Tasmania. Check serum calcium and 24 hour urine calcium.

**Diabetes insipidus (DI)**

Serum sodium and urea may be raised due to dehydration, but this is not always the case. Urine osmolality is low (less than that of plasma) as urine cannot be concentrated. Ask the patient to bring in a first morning urine and send to the laboratory for osmolality. Normal people usually have a high early morning urine osmolality (over 800 mosm/kg). If the osmolality is less than this and DI is suspected, a formal water deprivation test is required. Usually this would be arranged after consultation with an endocrinologist. A water deprivation test will also define whether the patient has renal or central DI. Note that the measurement of antidiuretic hormone (ADH) is not routinely offered and is rarely useful.

Central or neurogenic DI is usually associated with marked polyuria (>6 litres/day) whereas in renal DI, some concentrating capacity is usually preserved and urine volumes are often 3-4 litres/day.

**Lithium**

Figures vary, but about a third of patients taking lithium have polyuria. It is probably the most common cause of renal diabetes insipidus.

**Hypokalaemia**

Again the main cause of the polyuria is renal diabetes insipidus. Check for hyperadrenalism (if not on diuretics), by doing a renin/aldosterone ratio.

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**List of Causes:**

**Iatrogenic:**
- diuretic therapy
- alcohol (due to effects of alcohol and also large volume of fluid if a beer drinker)
- other drugs causing a renal DI, e.g. lithium, tetracyclines and many more.

**Hypothalamic-pituitary:**
- neurogenic diabetes insipidus –absent/decreased anti-diuretic hormone (ADH)
  - idiopathic
  - head injury
  - tumour
  - infection

**Renal:**
- renal DI-inability to respond to ADH
  - lithium and many other pharmacological agents
  - hypokalaemia
  - hypercalcaemia
  - chronic renal disease
  - pregnancy
  - congenital

- increased solute load per nephron (osmotic diuresis)
  - diabetes mellitus
  - hypercalcaemia
  - chronic renal failure
  - relief of chronic urinary obstruction (diuresis due to urea)

**Other:**
- compulsive water drinking

**Author:** Dr Ann Read

**Reference:**
Robert W. Schrier. Renal and Electrolyte Disorders
Sterile Pyuria

Pyuria is generally defined as the presence of at least $10^6$ leucocytes/L of uncentrifuged urine and is usually, but not always, associated with significant bacteruria (as demonstrated on culture). If routine bacteriological culture is negative the following should be considered.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Appropriate investigations</th>
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<tbody>
<tr>
<td>• Antibiotic treated UTI</td>
<td>Laboratory routinely tests for presence of antibacterial activity and reports</td>
</tr>
<tr>
<td>• Genital infection</td>
<td>Genital swabs / urine tests</td>
</tr>
<tr>
<td> Chlamydia trachomatis Neisseria gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td> Herpes simplex Trichomonas vaginalis</td>
<td></td>
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<tr>
<td> Gardnerella vaginalis</td>
<td></td>
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<tr>
<td>• Genitourinary tuberculosis</td>
<td>Early morning urines x3 for culture Tuberculin sensitivity testing (Mantoux)</td>
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<tr>
<td>• Renal calculi</td>
<td>Radiography</td>
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<tr>
<td>• Interstitial nephritis</td>
<td>Urine microscopy for dysmorphic red blood cells and eosinophils</td>
</tr>
<tr>
<td>• Neoplasia</td>
<td>Urine cytology</td>
</tr>
<tr>
<td>• Trauma</td>
<td></td>
</tr>
<tr>
<td>• False negative culture</td>
<td>Gram stain, select special media</td>
</tr>
<tr>
<td> eg. Haemophilus influenza, anaerobes, nutritionally deficient variants, slow growing organisms</td>
<td></td>
</tr>
</tbody>
</table>

Author: Dr John Roberts

### Antibiotic susceptibility results for commonly occurring causes of UTI

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>Amoxycillin</th>
<th>Augmentin</th>
<th>Cephalexin</th>
<th>Cotrimoxazole</th>
<th>Gentamicin</th>
<th>Norfloxacin</th>
<th>Trimethoprim</th>
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<tbody>
<tr>
<td>% Susceptible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>C. freundii</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>89.7</td>
<td>93.1</td>
<td>89.7</td>
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<td><strong>E. aerogenes</strong></td>
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<td>0</td>
<td>0</td>
<td>97.3</td>
<td>100</td>
<td>100</td>
<td>97.3</td>
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<tr>
<td><strong>E. cloacae</strong></td>
<td>0</td>
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<td>0</td>
<td>97.7</td>
<td>97.7</td>
<td>100</td>
<td>90</td>
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<td><strong>Enterococcus spp.</strong></td>
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<td>97.2</td>
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<td>N/A</td>
<td>N/A</td>
<td>0</td>
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<tr>
<td><strong>E. coli</strong></td>
<td>63.8</td>
<td>97.1</td>
<td>97.1</td>
<td>89.1</td>
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<td><strong>K. pneumoniae</strong></td>
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<td>96.7</td>
<td>96.7</td>
<td>93</td>
<td>98.7</td>
<td>98.1</td>
<td>87.3</td>
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<tr>
<td><strong>M. morganii</strong></td>
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<td>0</td>
<td>0</td>
<td>77.8</td>
<td>100</td>
<td>100</td>
<td>77.8</td>
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<td><strong>P. mirabilis</strong></td>
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<td>99.2</td>
<td>98.4</td>
<td>85</td>
<td>96.6</td>
<td>98.4</td>
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<td><strong>S. marcescens</strong></td>
<td>0</td>
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<td>0</td>
<td>61.5</td>
<td>92</td>
<td>84.6</td>
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<tr>
<td><strong>S. saprophyticus</strong></td>
<td>96</td>
<td>N/A</td>
<td>99</td>
<td>98.4</td>
<td>N/A</td>
<td>100</td>
<td>95.3</td>
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# Events Calendar 2007

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<tr>
<th>Month</th>
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<tr>
<td>March</td>
<td>Doctors’ Evening</td>
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<tr>
<td>March</td>
<td>Venepuncture Refresher Course</td>
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<tr>
<td>March</td>
<td>Practice Managers’ Meeting</td>
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<tr>
<td>July</td>
<td>Venepuncture Course</td>
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<tr>
<td>July</td>
<td>Receptionists’ Function</td>
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<tr>
<td>October</td>
<td>Practice Managers’ Evening</td>
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<tr>
<td>October</td>
<td>Doctors’ Evening</td>
</tr>
<tr>
<td>November</td>
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