best tests

July 2015

Monitoring diabetes before, during and after pregnancy

Asymptomatic bacteriuria and urinary tract infections (UTIs) in older people

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better medicine

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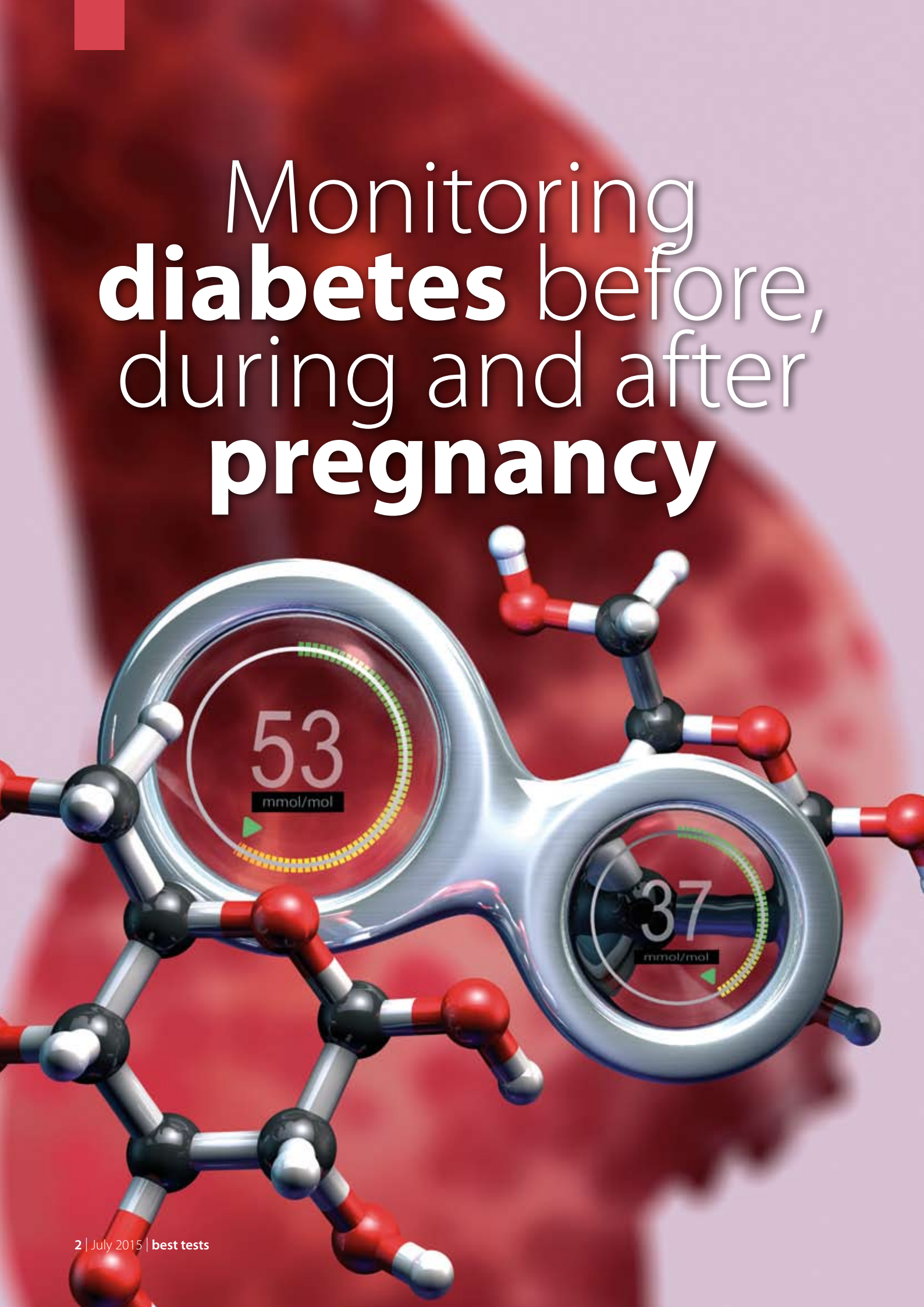
13 The New Zealand Laboratory Schedule and Test Guidelines: Immunology Tests

Over the last few editions of Best Tests we have outlined the various sections of the New Zealand Laboratory Schedule. The aim of this Schedule is to provide clinicians with consistent guidance when considering requesting laboratory tests and to ensure the uniform availability of tests across District Health Boards (DHBs) in the future. The final section of the series focuses briefly on immunology testing.

14 A pragmatic guide to asymptomatic bacteriuria and testing for urinary tract infections (UTIs) in people aged over 65 years

Asymptomatic bacteriuria and urinary tract infections (UTIs) frequently occur in people aged over 65 years. Bacteriuria in older people without urinary symptoms, i.e. asymptomatic bacteriuria, is generally harmless and does not need to be routinely treated. Diagnosing and managing UTIs is more difficult in older patients as long-term urinary conditions (e.g. incontinence) or genitourinary abnormalities (e.g. anterior vaginal prolapse) are more common. The patient's symptoms and signs are the strongest predictor of a UTI and clinical information should always be included on laboratory requests for urine culture as it will influence the interpretation of results and how the patient is subsequently managed. Guidance on the investigation of suspected UTIs varies depending on whether the patient is female, male or if they have a urinary catheter. Antibiotic treatment for uncomplicated UTIs can often be initiated empirically, but local susceptibility data is crucial to guide the choice of antibiotic.

Monitoring **diabetes** before, during and after **pregnancy**



Hyperglycaemia during pregnancy is associated with a range of adverse outcomes which can affect both mother and child, and can occur during pregnancy, childbirth or later in life. Due to physiological changes associated with pregnancy, women are at increased risk of developing diabetes, or having worsening glycaemic control if they have pre-existing diabetes. In December, 2014, the Ministry of Health released the Screening, Diagnosis and Management of Gestational Diabetes in New Zealand clinical practice guideline and some changes to testing for gestational diabetes are recommended. In this article, we summarise the recent Ministry of Health guidelines, with a focus on the role of the general practitioner in testing for undiagnosed diabetes early in pregnancy and monitoring for the development of type 2 diabetes after pregnancy.

What is new?

- All pregnant women should be tested for undiagnosed diabetes using HbA_{1c} prior to 20 weeks' gestation
- Pregnant women with $HbA_{1c} \geq 50$ mmol/mol should be referred to a diabetes in pregnancy clinic
- Pregnant women with HbA_{1c} 41 – 49 mmol/mol should be offered lifestyle advice to reduce risks of adverse maternal and fetal outcomes; local protocols may recommend that these women are also referred to a diabetes in pregnancy clinic
- At 24 to 28 weeks' gestation, women are recommended to undergo an oral glucose tolerance testing regimen, which is dependent on their initial HbA_{1c} result
- HbA_{1c} is used to monitor glycaemia postpartum in women who have had gestational diabetes, beginning at three months after birth

Pregnancy is a time of significant metabolic change when a woman's physiology adapts to meet the challenges of gestation. Insulin sensitivity is decreased by as much as 50 to 60% during pregnancy, a level comparable to that seen in people with type 2 diabetes or impaired glucose tolerance.[1] This change in insulin sensitivity is thought to be caused by endocrine signals from the growing placenta, and has evolved to aid fetal development.[2] During pregnancy the mother's pancreas typically responds with beta-cell and islet hyperplasia to enable greater insulin production and regulate blood glucose levels.[1] Women who do not produce enough insulin to compensate for this transitory increase in insulin resistance develop gestational diabetes. These women often have risk factors for the development of type 2 diabetes and a higher level of insulin resistance before pregnancy.[1] After childbirth, the insulin resistance associated with pregnancy usually resolves, as does the need for treatment, if this has been required.

Maternal hyperglycaemia during pregnancy leads to fetal overgrowth (macrosomia), which is associated with an increased risk of difficulties in delivery (shoulder dystocia, third or fourth degree perineal tears, postpartum haemorrhage) and also a higher rate of caesarean section. Both maternal obesity and excessive gestational weight gain can cause macrosomia, independently of gestational diabetes. The more serious complications, such as congenital malformation and stillbirth, are largely confined to those women with previously unrecognised diabetes (usually type 2) that has come to light as "gestational diabetes" (Table 1, over page).

Pregnant women with intermediate glycaemia but without diabetes are also at risk of the same adverse outcomes

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study assessed the association of glucose tolerance with pregnancy outcomes in over 25,000 pregnant women in nine countries who were below the diagnostic threshold for diabetes.[3] Increasing maternal glycaemia was associated with an increased risk of the infant being above the 90th centile of birth weight and pre-eclampsia. There were modest associations with increased risks of neonatal hypoglycaemia, caesarean delivery, premature delivery, shoulder dystocia or birth injury, and the infant requiring neonatal intensive care.[3] This study shows that increasing glycaemia, even if below the threshold for diagnosis of gestational diabetes, is potentially detrimental to the fetus. The lowest risk pregnancy in terms of maternal glycaemia is one where the mother has blood glucose levels as close to normoglycaemic as possible; in this study the lowest risk category was mothers with results on a 75 g oral glucose tolerance test of fasting plasma glucose ≤ 4.2 mmol/L, one hour glucose levels ≤ 5.8 mmol/L or two hour glucose levels ≤ 5.0 mmol/L.[3]

Which women are most at risk of diabetes during pregnancy?

Females with any of the following characteristics are at increased risk of undiagnosed diabetes or developing diabetes during pregnancy:[4]

- A personal history of gestational diabetes or intermediate hyperglycaemia
- A previous infant > 4 kg at birth
- Increasing maternal age, particularly age over 35 years
- A first degree relative with diabetes
- A body mass index (BMI) ≥ 27 kg/m^2 in an Indo-Asian person or ≥ 30 kg/m^2 in other ethnicities
- Polycystic ovary syndrome
- Cardiovascular disease, hypertension, or elevated total cholesterol
- Physical inactivity
- Excessive gestational weight gain
- Long-term use of steroid (glucocorticoid) or antipsychotic medicines
- Acanthosis nigricans (hyperpigmentation of the skin)

The incidence of diabetes in pregnancy in New Zealand

The prevalence of diabetes has increased in New Zealand over recent decades and is currently around 5.8%; approximately 90% of whom are people with type 2 diabetes.[4, 7] Data from the New Zealand Adult Nutrition Survey 2008/09 show that 1.5 – 1.8% of women aged between 25 and 44 years reported a diagnosis of diabetes with another 1.1 – 2.0% having previously undiagnosed diabetes, highlighting that for every woman around childbearing age with diagnosed diabetes there is another with undiagnosed diabetes.[8] In New Zealand from 2001 to 2012 there was an annual increase of 13.9%

Table 1: Adverse outcomes for mothers with hyperglycaemia during pregnancy and their children[4, 5]

Diabetes during pregnancy increases the risk of adverse outcomes for women:	**Diabetes during pregnancy increases the risk of adverse outcomes for infants:**
Complications during pregnancy: ■ Hypertension ■ Polyhydramnios ■ Pre-term labour Complications during labour: ■ Shoulder dystocia ■ Operative vaginal delivery ■ 3rd and 4th degree perineal tear ■ Caesarean section ■ Postpartum haemorrhage In later life: ■ Type 2 diabetes	Major complications with previously unrecognised diabetes: ■ Stillbirth ■ Congenital malformation ■ Miscarriage ■ Perinatal death Fetal development complications: ■ Macrosomia* ■ Large for gestational age* Birth traumas and complications during and after birth: ■ Shoulder dystocia ■ Bone fractures ■ Brachial plexus palsy ■ Hypoglycaemia ■ Hyperbilirubinaemia ■ Neonatal hypoglycaemia
Women with intermediate glycaemia have an increased risk of: ■ Caesarean section ■ Premature delivery ■ Shoulder dystocia or birth injury ■ Pre-eclampsia	**Infants born to women with intermediate glycaemia have an increased risk of:** ■ Large for gestational age ■ Neonatal hypoglycaemia ■ Shoulder dystocia or birth injury ■ Intensive neonatal care ■ Hyperbilirubinaemia

* Macrosomia is defined as a large neonate regardless of gestational age, with cut-offs of 4000 g or 4500 g often used. Large for gestational age defines neonates with a birth weight above the 90th centile for gestational age.[6]

in the rate of gestational diabetes, with 4.9% of expectant mothers affected in 2012.[4] It is not known how many pregnancies in New Zealand are to mothers with pre-existing diabetes. Increases in the rates of gestational diabetes and type 2 diabetes are likely to be due to changes in shared risk factors, such as physical inactivity and obesity.

There are marked differences in the rate of gestational diabetes between ethnicities in New Zealand: Asian (8.1%), Middle Eastern, Latin American and African (7.5%), Pacific (7.2%), Māori (3.3%) and European (3.3%).[4] However, it has been suggested that the lower recorded rate among Māori may be due to lower rates of testing.[4] Rates appear to be increasing more rapidly in the Auckland and Northland regions.[4]

Testing for glycaemia pre-conception

In women with known diabetes or those with a previous history of gestational diabetes, the ideal scenario is for pregnancies to be planned and glycaemic control prior to pregnancy to be as optimal as possible.

Women with a history of gestational diabetes are at high risk of a having gestational diabetes during a subsequent pregnancy. Rates of recurrence from 30% to 84% have been reported, with the highest rates in women who needed insulin treatment during their previous pregnancy.[4] For women with a previous history of gestational diabetes who report that they wish to become pregnant, HbA_{1c} levels should be checked and lifestyle modification encouraged where appropriate so that their pregnancy begins with blood glucose levels as close to normoglycaemic as possible.

Women with established diabetes are at higher risk of adverse pregnancy outcomes such as congenital malformation, miscarriage, stillbirth and perinatal death (Table 1).[4, 5] Ideally, women with diabetes should use contraception until blood glucose control is established and then attempt to conceive while maintaining good blood glucose control.[5] Folate supplementation to reduce the risk of neural tube defects is recommended for all women who are trying to get pregnant, from one month before to 12 weeks after conception. Women with diabetes are recommended to take 5 g of folic acid daily (most other women can take 800 micrograms daily.[9]

For further information on pre-conception care in general practice, see: "A healthy start", BPJ 67 (Apr, 2015), available from: **www.bpac.org.nz/BPJ/2015/April/healthy-start.aspx**

Early pregnancy: the role of primary care in testing for diabetes

Recommendations for testing and diagnosis of diabetes in pregnant women have been the subject of much debate (see: "A lack of evidence hampers consensus on how to test for gestational diabetes", over page). Despite the lack of consensus on testing during pregnancy to identify women with gestational diabetes, the role of testing early in pregnancy and postpartum in women with previous gestational diabetes is much clearer:[4, 5]

- There is good evidence that hyperglycaemia in early pregnancy resulting from undiagnosed diabetes (usually type 2) results in adverse pregnancy outcomes and that treatment of women with diabetes during pregnancy improves the health of mother and child
- There is good evidence that women with a history of gestational diabetes are at increased risk of future type 2 diabetes

There is, therefore, a sound evidence base to test for undiagnosed diabetes in women who become pregnant, in order to identify those who can benefit from intervention, and for women who have had gestational diabetes to be monitored postpartum and be offered advice and support to reduce their future risk of type 2 diabetes.

Ministry of Health guidelines now recommend that all women should be tested for undiagnosed diabetes early in pregnancy (prior to 20 weeks' gestation) using HbA_{1c}. A schedule of oral glucose tolerance tests (OGTT) between 24 to 28 weeks' gestation to detect gestational diabetes is also recommended, with the specific testing regimen dependent on the HbA_{1c} test result from early pregnancy (Figure 1).[4]

Testing for undiagnosed diabetes in early pregnancy

Key practice points:

- It is now recommended that **all pregnant women undergo testing for pre-existing diabetes**
- Use HbA_{1c} prior to 20 weeks' gestation to detect pre-existing diabetes
- Women with an $HbA_{1c} \geq 50$ mmol/mol should be referred to a diabetes in pregnancy clinic (Figure 1).
- Women with an HbA_{1c} between 41 and 49 mmol/mol should be encouraged to adopt lifestyle measures to reduce their risk of adverse pregnancy outcomes; local DHB protocols may vary as to whether to refer these women to a diabetes in pregnancy clinic

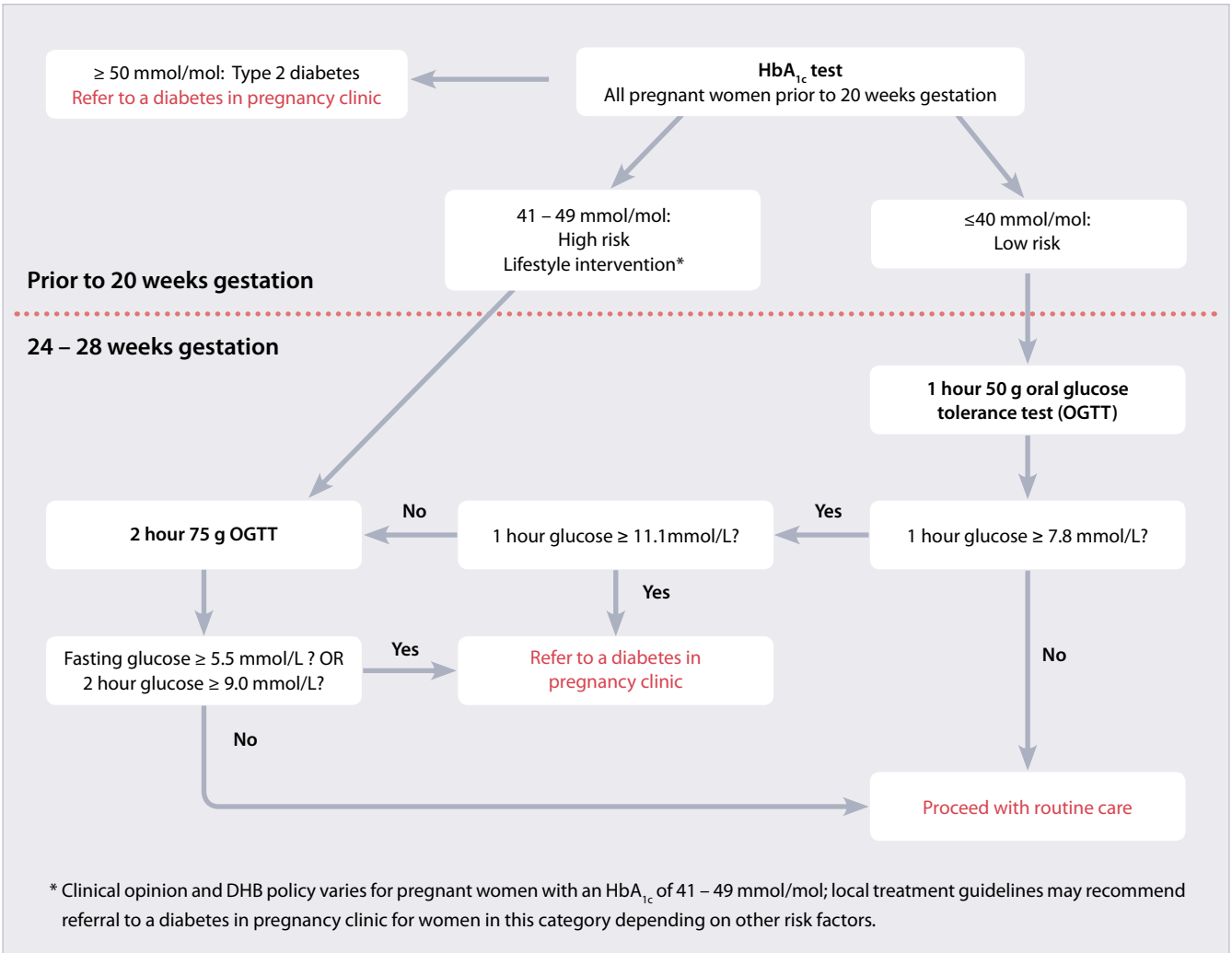


Figure 1: Screening and testing pathways for diagnosing diabetes in pregnancy[4]

Testing for pre-existing diabetes can be performed using HbA_{1c}. Physiological changes which occur during pregnancy cause red blood cell turnover to increase and HbA_{1c} levels decline, so HbA_{1c} should be performed prior to 20 weeks' gestation to improve accuracy.[4] Whenever testing for diabetes using HbA_{1c}, clinicians should keep in mind that some clinical conditions can affect HbA_{1c} levels and give misleading results (see: Factors affecting the reliability of HbA_{1c} testing, over page).

HbA_{1c} test is most easily done as part of the first antenatal blood test screen. If a patient is seen in general practice after they have enrolled with a lead maternity carer (LMC), check that the first antenatal screen, including HbA_{1c}, has been completed.

HbA_{1c} testing in early pregnancy will identify women with probable pre-existing diabetes (HbA_{1c} ≥50 mmol/mol) but also creates a new diagnostic entity – that is women with an HbA_{1c} of 41 to 49 mmol/mol. The HAPO study showed that mothers with elevated glycaemia below the threshold for diagnosing diabetes are at risk of some adverse pregnancy outcomes so these women should be encouraged to adopt lifestyle measures to reduce their risk of developing gestational diabetes and the adverse pregnancy outcomes associated with elevated glycaemia (see: "Lifestyle approaches", Page 9).

A recently published opinion piece argues that women with an HbA_{1c} ≥ 41 mmol/mol should be referred immediately for management to a diabetes in pregnancy clinic (rather than just those with an HbA_{1c} ≥ 50 mmol/mol).[15] There is as yet no evidence from randomised controlled trials, however, that earlier pharmacological intervention in these pregnancies improves outcomes (see: "Research into gestational diabetes testing in New Zealand", Page 11).

Caring for patients with pre-existing diabetes who become pregnant

With rates of both type 1 and type 2 diabetes increasing in New Zealand, and maternal age at pregnancy increasing, it is becoming more likely that clinicians will have under their care women with diabetes who become pregnant. In addition to blood glucose monitoring with the aim of meeting recommended treatment targets (see: "What are the treatment targets?", Page 9) these women usually require extra testing during pregnancy, in particular for retinopathy and nephropathy.

Retinopathy testing

Diabetic retinopathy can progress during pregnancy.[5] Women with diabetes who become pregnant should undergo retinal photography during the first trimester, unless they have had this performed in the previous three months.[5] Follow-up ophthalmology examinations during pregnancy may be indicated depending on the degree of retinopathy.

Renal testing

Nephropathy during pregnancy is associated with an increased risk of pre-eclampsia, fetal growth restriction and pre-term birth. Ideally, women with pre-existing diabetes should have renal function tests performed in the three months prior to pregnancy, or if not, early in pregnancy at the first point of contact with the clinician.[5] A protein:creatinine level of 30 mg/mmol reflects a daily protein excretion of 300 mg and is the recommended test for the presence of proteinuria in pregnancy.[18] A serum creatinine level > 90 micromol/L accompanied by hypertension after 20 weeks' gestation is diagnostic of pre-eclampsia.[18]

For further information on other routine laboratory testing during pregnancy, see: **www.bpac.org.nz/BT/2011/July/pregnancy.aspx**

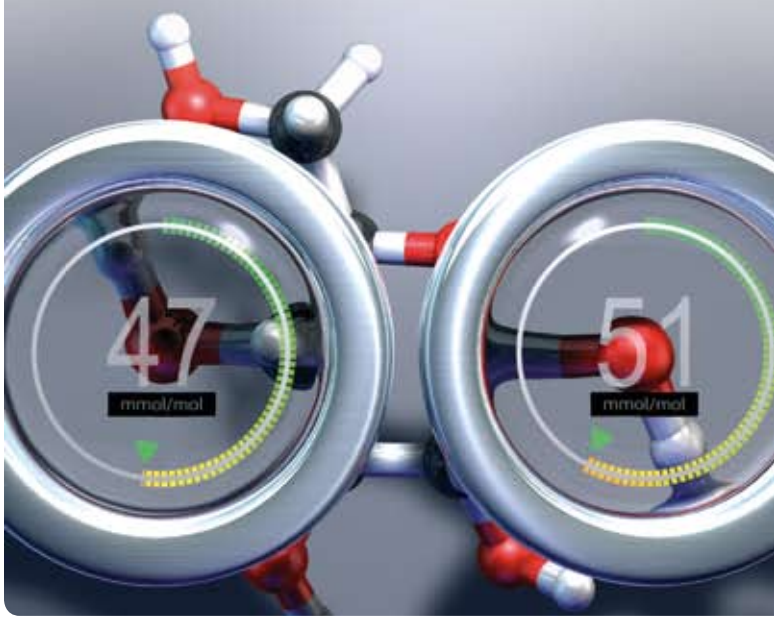
Later in pregnancy: testing and management is organised by the LMC and diabetes in pregnancy clinic

Ministry of Health guidelines now recommend that oral glucose testing later in pregnancy (at 24 to 28 weeks) be tailored to the patient's early HbA_{1c} results. This testing would usually be organised by the midwife. Most women will be at low risk of developing gestational diabetes and can undergo a 50 g oral glucose challenge test. This test has a good negative predictive value, so that women who test negative are at low risk of developing hyperglycaemia and the associated risks of adverse pregnancy outcomes. Therefore, for most women

A lack of evidence hampers consensus on how to test for gestational diabetes

In general there is a low quality of evidence available to guide recommendations for testing for hyperglycaemia in pregnancy; in particular, which screening strategies result in the best health outcomes for mother and child at the end of pregnancy has not been thoroughly assessed.[4] As a result, recommendations for how to test for hyperglycaemia during pregnancy vary, principally for which type of oral glucose tolerance test to perform during pregnancy and what glucose level cut-offs should be adopted to identify patients with gestational diabetes.[4, 10] In New Zealand, testing rates have been noted to vary across District Health Boards.[11] A National Gestational Diabetes Mellitus Technical Working Party published recommendations in 2008 to encourage alignment and standardisation across the country.[11]

The Maternity Quality Initiative Expert Working Group, formed in 2009 by the Ministry of Health, identified a need for evidence-based guidelines for the diagnosis and management of hyperglycaemia in pregnancy in New Zealand.[12] These guidelines were developed by a multidisciplinary team and published by the Ministry of Health in December 2014. The recommendations in this guideline differ from those published by other sources: for example, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (July, 2014) and Australasian Diabetes in Pregnancy Society (November, 2014) recommendations.[13, 14]



Factors affecting the reliability of HbA_{1c} testing

Measuring HbA_{1c} is an indirect method of testing glycaemia; it relies on the glycation of haemoglobin over the lifespan of an erythrocyte rather than directly measuring levels of glucose in the blood. Various clinical conditions can affect erythropoiesis or erythrocyte destruction and influence haemoglobin levels or lifespan, or can affect the chemical reactions which cause glycation of haemoglobin or used in assays to measure HbA_{1c}.[16] The best workaround for clinicians when confronted with HbA_{1c} results which do not appear to line up with a patient's presentation is to avoid the problems of indirect testing by simply ordering a blood glucose test; either a fasting plasma glucose > 7 mmol/L or a random plasma glucose > 11.1 mmol/L can be used to diagnose diabetes.[17]

Patients with haemoglobinopathies may have altered HbA_{1c} results depending on the type of assay used, with the direction of change depending on the specific diagnosis. Other factors which may potentially give erroneous HbA_{1c} results include:[16]

- Factors which can increase HbA_{1c}:
  - Alcohol intake
  - Iron or vitamin B_{12} deficiency
  - Hyperbilirubaemia
  - Renal failure
  - Opiate use
  - Splenectomy
- Factors which can decrease HbA_{1c}:
  - Erythropoietin, iron or vitamin B_{12} administration
  - Ingestion of antioxidants such as vitamin C or E
  - Very high triglyceride levels
  - Chronic aspirin use
  - Splenomegaly
  - Rheumatoid arthritis
  - Use of antiretrovirals

the burden of testing is limited to a one hour test. Women who test positive on the 50 g oral glucose challenge should undergo a 75 g two hour oral glucose tolerance test.

Women who are at increased risk of developing gestational diabetes (initial HbA_{1c} results of 41 – 49 mmol/mol) should proceed directly to a 75 g two hour oral glucose tolerance test without undergoing an initial 50 g oral glucose challenge test (Figure 1).

There is some disagreement as to whether women with additional risk factors should proceed straight to a 75 g oral glucose tolerance test even if their initial HbA_{1c} screening result is ≤ 40 mmol/mol. For example, there is concern that an obese woman may test negative on a 50 g glucose challenge as the glucose amounts are not adjusted for body weight, potentially missing a diagnosis.[15]

Women who have pre-existing diabetes or have probable undiagnosed diabetes detected with initial HbA_{1c} screening should be under the care of a diabetes in pregnancy team. Further oral glucose tolerance testing is unlikely to be indicated.

One scenario which is not covered by the Ministry of Health guidelines is which testing procedure should be performed for women who do not have an initial HbA_{1c} result available. Given that an HbA_{1c} test can be ordered with the first antenatal blood tests it is likely that women without an HbA_{1c} measurement in early pregnancy also have a lower level of engagement with health services, and as a result may be at increased risk of adverse pregnancy outcomes. A reasonable course of action would be to request that these women undergo a 75 g two hour oral glucose tolerance test.

Women with diabetes during pregnancy may require oral hypoglycaemic medicines or insulin

Women who have difficulty reaching blood glucose targets or who have high initial blood glucose levels at diagnosis are likely to require hypoglycaemic medicines, such as metformin or insulin injections (see: "What are the treatment targets?"). The regimen of medicines used to control the patient's blood glucose levels will be determined by the diabetes in pregnancy clinic, tailored to their treatment preferences and the degree of hyperglycaemia.[5, 20] Metformin is the preferred first-line treatment, as the risk of hypoglycaemia is lower than when using insulin and many patients prefer the ease of taking a tablet rather than using injections. Glibenclamide is recommended as a possible second-line oral hypoglycaemic

medicine by the Ministry of Health and National Institute for Health and Care Excellence, where blood glucose control is insufficient with metformin and the mother is unwilling or unable to use insulin, or if she experiences intolerance to metformin.[4, 5] Patients using only metformin have better outcomes than those using only glibenclamide.[4, 5]

Women with gestational diabetes should self-monitor blood glucose

Self-monitoring and laboratory measurement of glucose levels during pregnancy are used as the key tests to guide treatment, not HbA_{1c}. While HbA_{1c} is useful for monitoring long-term blood glucose control in non-pregnant patients, it does not capture fluctuations in glucose concentrations, and evidence suggests that targeting treatment to postprandial glucose levels results in the best outcomes for both mother and child in gestational diabetes. Furthermore, physiological changes affect HbA_{1c} levels during pregnancy, causing mean levels to drop compared with non-pregnant women for the same degree of hyperglycaemia.[4, 5]

What are the treatment targets?

Recommended treatment targets for self-monitored (capillary fingerprick) blood glucose levels are:[4, 20]

- Pre-prandial (fasting): ≤ 5.0 mmol/L
- Post-prandial, either ≤ 7.8 mmol/L at one hour or ≤ 6.7 mmol/L at two hours

Ministry of Health guidelines recommend that women with gestational diabetes should aim to have > 90% of blood glucose measurements in a week fall within the targets for glucose levels. If more than 10% of measurements fall outside of these ranges, treatment should be reassessed.[4]

Research suggests that the closer to normal blood glucose is during pregnancy, the lower the risk of maternal and neonatal complications. The treatment of all types of diabetes is a balancing act between attaining good glycaemic control while minimising the risk of hypoglycaemia. Maintaining blood sugars that are too low can cause intrauterine growth restriction.[5, 20]

Lifestyle approaches are the cornerstone of reducing the risk and burden of diabetes in all people

A healthy diet and regular exercise are the cornerstones of preventing hyperglycaemia in all people, regardless of whether they are pregnant. All women with diabetes during pregnancy should be offered specialist dietary advice.[4] A combined dietary and exercise approach is recommended which emphasises a balanced, healthy diet and encourages patients to be active for at least 30 minutes a day most days of the week unless there are clinical contraindications to physical activity. Limiting strenuous exercise may be necessary as pregnancy progresses and women should consult with their LMC or diabetes in pregnancy team regarding appropriate physical activity.

A key goal is to limit gestational weight gain in those who are already overweight. The United States Institute of Medicine released guidelines in 2009 for healthy ranges of weight gain during pregnancy depending on a woman's pre-pregnancy body mass index (BMI) (Table 2).[19] Women who gain more than these amounts are at increased risk of developing gestational diabetes, pregnancy-associated hypertension, complications during delivery and postnatal outcomes such as subsequent weight retention after pregnancy and unsuccessful breastfeeding.[19] Infants born to mothers with excessive weight gain during pregnancy are at an increased risk of neonatal mortality, being large for gestational age, and subsequent development of childhood obesity.[19]

Table 2: Recommended ranges of weight gain for pregnant women* [19]

Pre-pregnancy BMI (kg/m^2)	Rate of weight gain in 2nd and 3rd trimester (kg per week)	Total weight gain (kg)
< 18.5	0.44 – 0.58	12.5 – 18
18.5 – 24.9	0.35 – 0.50	11.5 – 16
25.0 – 29.9	0.23 – 0.33	7 – 11.5
≥ 30	0.17 – 0.27	5 – 9

* N.B. These ranges are for singleton pregnancies. Larger increases in weight are acceptable for women with multiple fetuses.

After pregnancy: general practitioners should reassess glycaemic status

Following a pregnancy affected by gestational diabetes, maternal hyperglycaemia may either resolve completely, or persist – either as intermediate hyperglycaemia or as established diabetes.

Women with previous gestational diabetes have an approximately six to eight-fold higher risk of developing type 2 diabetes than women who have been pregnant without diabetes, and may be at increased risk of developing type 1 diabetes.[4, 5] Five year incidence rates of type 2 diabetes of 18% to 50% have been reported in women with a history of gestational diabetes.[21] The best approach is for preventive measures to begin as soon as the mother can manage.

HbA_{1c} testing at three months postpartum or later is recommended

Clinicians should aim to assess the glycaemic status of all women who have had gestational diabetes. Research suggests that many women with a history of gestational diabetes in New Zealand are not subsequently tested.

Oral glucose tolerance testing at six weeks after birth has been, until recently, the recommended way to assess glycaemic status following gestational diabetes, and this is still recommended in many overseas' guidelines. However, the Ministry of Health guidelines now recommend using HbA_{1c} at three months after birth, with the possible addition of fasting blood glucose. It is hoped that this change will facilitate greater uptake of testing given that many patients find the oral glucose tolerance test inconvenient. This change also means that three month postnatal testing uses the same test as later annual monitoring, so that clinicians are better able to determine if glycaemic control has deteriorated.[4]

Annual testing thereafter using HbA_{1c} is recommended (Table 3). Opportunistic or scheduled patient appointments, such as seeing the clinician when they bring their infant for vaccinations, can be a good time to test the mother for diabetes, or clinicians can set up an electronic reminder to ensure HbA_{1c} testing is performed at appropriate intervals. Patient reminders such as a letter, email or text are likely to improve rates of postpartum testing for diabetes.[22]

Testing HbA_{1c} at three months postpartum has low sensitivity but high specificity for detecting type 2 diabetes in women who have had gestational diabetes compared to a 75 g oral glucose tolerance test. It is likely to detect those with the highest levels of glycaemia and most in need of treatment. Fasting blood glucose testing can also be performed at three months postpartum at the clinician's discretion, which increases the sensitivity of three month testing for detecting patients with type 2 diabetes.[4]

Table 3: Tests and appropriate follow-up at three months postpartum for women who have had gestational diabetes[4]

HbA_{1c} level (mmol/mol) at three months	Diagnosis or risk category	Patient care and testing
≥ 50 and with symptoms of diabetes	Diabetes*	Proceed to treat and follow-up as per diabetes guidelines
≥ 50 and asymptomatic	Possible diabetes*	Repeat testing with HbA_{1c} or fasting blood glucose
41 – 49	High risk of diabetes*	Provide diabetes prevention advice regarding diet and exercise measures. Metformin treatment may be considered. (see: "Patient and clinician actions that can prevent future diabetes") Re-test HbA_{1c} in six months and then annually thereafter
≤ 40	Medium risk of diabetes*	Annual HbA_{1c} testing

* In most cases this will be type 2 diabetes; occasionally patients with early stage type 1 diabetes or rarely monogenic diabetes (caused by single gene mutations) may be encountered.

Patient and clinician actions that can prevent future diabetes

Lifestyle measures are the cornerstone of preventing and treating type 2 diabetes and clinicians should encourage women with a previous history of gestational diabetes to adopt a diet and exercise regimen which can reduce their risk of future diabetes. In addition to lifestyle measures, other advice and treatments which clinicians can offer include:

Breastfeeding: Mothers who breastfeed usually lose more weight than mothers who do not, and various cohort and observational studies have found that mothers who have breastfed have reduced risks for a number of metabolic diseases across their lifetime, including obesity, diabetes, hypertension, hyperlipidaemia and cardiovascular disease.[23]

Metformin: Women with an HbA_{1c} of 41 – 49 mmol/mol who have not been successful in reducing their level of glycaemia with lifestyle measures could be offered metformin.[4] Data from the United States Diabetes Prevention Program study suggests a number needed to treat (NNT) of seven patients for ten years to prevent one case of type 2 diabetes.[24] Clinicians may wish to consult an endocrinologist or diabetes specialist when considering this treatment approach.

Research into gestational diabetes testing in New Zealand

The gestational diabetes mellitus study of detection thresholds (GEMS) study

Clinicians in any area of New Zealand may consider referring their pregnant patients to the GEMS study, currently being conducted by the Liggins Institute at the University of Auckland. This study aims to randomise pregnant females to undergo testing and treatment according to the New Zealand criteria for the diagnosis of gestational diabetes or the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria in order gather better evidence regarding which criteria produce the best outcomes for mother and child. The IADPSG recommend diagnosing gestational diabetes at lower cut-offs of oral glucose tolerance test results than the New Zealand guidelines.

For further information, see: **www.ligginstrials.org/GEMS** or email: **gems@auckland.ac.nz**

The "Pre-diabetes in pregnancy: can early intervention improve outcomes" (PINTO) trial

The aim of the PINTO trial is to examine whether blood glucose monitoring and initiating treatment for hyperglycaemia in women with HbA_{1c} levels between 41 – 49 mmol/mol in early pregnancy, can improve health outcomes compared with lifestyle advice and follow up gestational diabetes screening at 24 – 28 weeks' gestation. The first phase of the trial is a feasibility study which will inform the main randomised controlled trial.

Researchers will be recruiting women in the National Woman's Hospital (Auckland) or Christchurch Women's Hospital catchment areas from 1 October, 2015. General practitioners in these areas should refer women with an $HbA_{1c} \geq 41$mmol/mol directly to their local diabetes in pregnancy clinic as soon as possible, where dietary and weight gain advice, triage, and consent will take place. A mail out to general practitioners will take place prior to this date, to provide further information about the study.

It is hoped that this study will show that early intervention in this patient group, including blood glucose monitoring and optimisation of blood glucose levels through dietary measures and medicines as required, will reduce pre-eclampsia, neonatal morbidity and mortality without causing harm. It is also hoped that the study will reduce inequalities in health-related outcomes for Māori and Pacific women, who have high rates of pre-diabetes and are the least likely to take up conventional screening for gestational diabetes.

For further information about PINTO, contact Dr Ruth Hughes: **ruth.hughes@cdhb.health.nz**

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The New Zealand Laboratory Schedule and Test Guidelines: Immunology Tests

Over the last few editions of Best Tests we have outlined the various sections of the New Zealand Laboratory Schedule. The aim of this Schedule is to provide clinicians with consistent guidance when considering requesting laboratory tests and to ensure the uniform availability of tests across District Health Boards (DHBs) in the future. The final section of the series focuses briefly on immunology testing.

The Guidelines for immunology testing were developed by the Immunology subgroup, chaired by Dr Richard Steele. The group included a number of immunologists and allergy specialists from throughout New Zealand. Tests in the Schedule are divided into Tier 1, which all referrers can order, and Tier 2, meaning that the test must be ordered in conjunction with another health professional with a particular area of expertise. For some tests, additional clinical guidance is provided.

For further information on the New Zealand Laboratory Schedule see: **www.dhbsharedservices.health.nz/Site/Laboratory/Laboratory-Schedule-Review-Project.aspx**

Immunology tests

The immunology tests in the Laboratory Schedule were considered in the following categories:

- Allergy
- Autoimmune tests – ANCA
- Serological and genetic tests for coeliac disease
- Complement
- Infection
- Immunodeficiency
- Tests not funded

Many immunology tests are Tier Two tests

Immunological testing includes a wide range of tests which can have clinical relevance in a number of conditions including autoimmune disorders, immune deficiencies, malignancy, inflammatory disorders and allergic disease. Many of the tests in the immunology section of the Laboratory Schedule are defined as Tier Two and therefore should be ordered and interpreted with the assistance of a specialist in the particular clinical field. Interpretation of tests defined as Tier One often also requires discussion with a relevant specialist, e.g. an immunologist or rheumatologist.

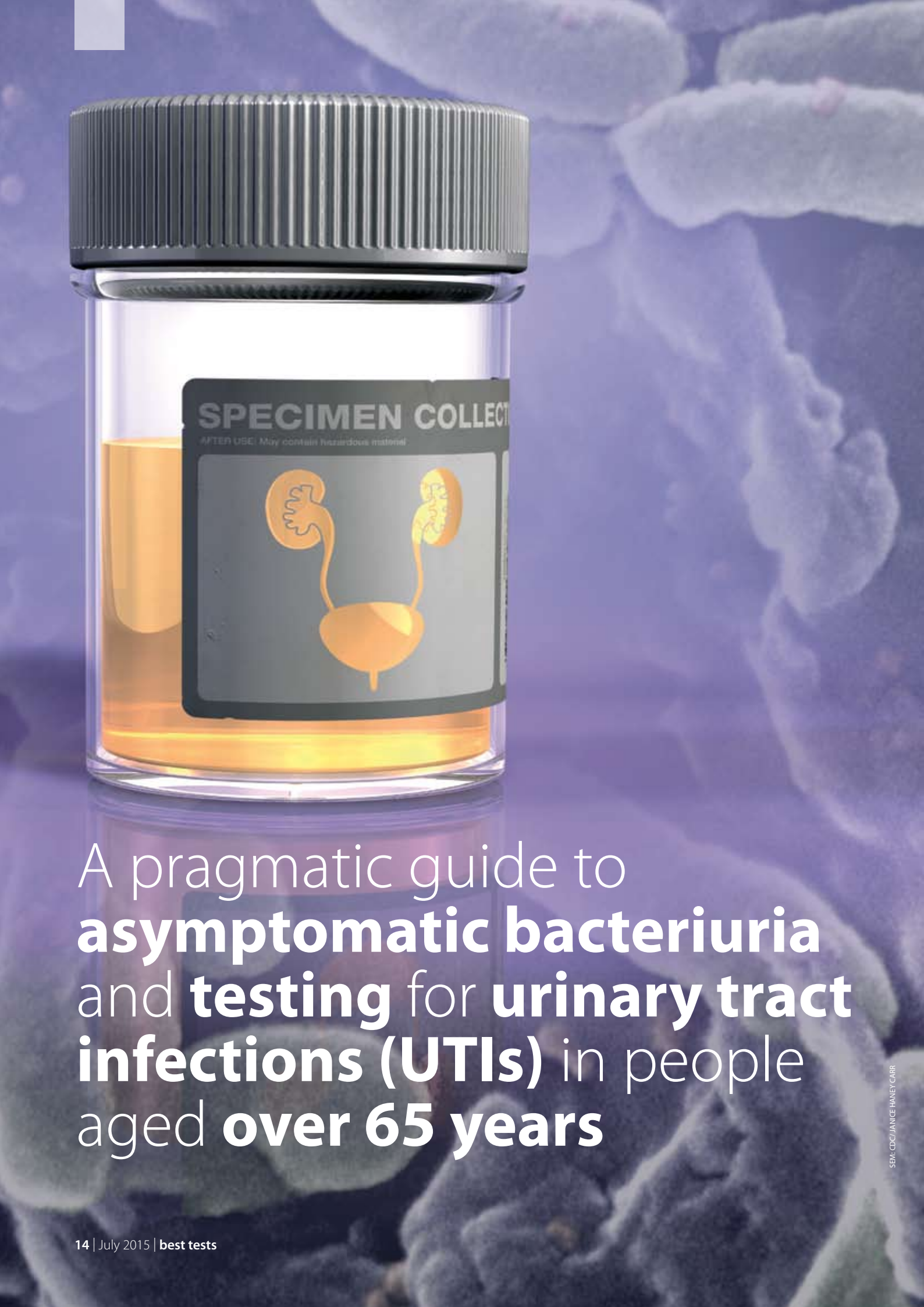
Gliadin antibody tests are no longer funded (including native anti-gliadin antibody)

Gliadin antibody testing is now regarded as being unnecessary for the diagnosis of coeliac disease or "gluten sensitivity" and the test is no longer funded in New Zealand. Although this test was initially important and one of the few widely available tests for coeliac disease during the 1980s, testing using IgA tissue transglutaminase test is the now the preferred initial method in primary care.

Guidance has been developed for anti-neutrophil cytoplasmic antibody testing

A brief guideline has been developed which lists the vasculitic conditions in which anti-neutrophil cytoplasmic (ANCA) testing is indicated. The results of ANCA testing may be misleading if there is co-existing infection or conditions not included amongst those indicated in the guideline. ANCA testing is non-specific and confirmation of a diagnosis of a vasculitic condition often requires a tissue biopsy or discussion with a relevant specialist.

The complete series of bpac^{nz} articles on the New Zealand Laboratory Schedule and Test Guidelines has been compiled into a virtual handbook, available online at: **www.bpac.org.nz/Series**



A pragmatic guide to **asymptomatic bacteriuria** and **testing** for **urinary tract infections (UTIs)** in people aged **over 65 years**

SEM: CDC/ JANICE HANEY CARR

Asymptomatic bacteriuria and urinary tract infections (UTIs) frequently occur in people aged over 65 years. Bacteriuria in older people without urinary symptoms, i.e. asymptomatic bacteriuria, is generally harmless and does not need to be routinely treated. Diagnosing and managing UTIs is more difficult in older patients as long-term urinary conditions (e.g. incontinence) or genitourinary abnormalities (e.g. anterior vaginal prolapse) are more common. The patient's symptoms and signs are the strongest predictor of a UTI and clinical information should always be included on laboratory requests for urine culture as it will influence the interpretation of results and how the patient is subsequently managed. Guidance on the investigation of suspected UTIs varies depending on whether the patient is female, male or if they have a urinary catheter. Antibiotic treatment for uncomplicated UTIs can often be initiated empirically, but local susceptibility data is crucial to guide the choice of antibiotic.

Asymptomatic bacteriuria is not necessarily bad bacteria

It is a common misconception that urine from a healthy person is sterile. In reality bacteria from the gastrointestinal tract can readily enter the bladder via the urethra. Once in the bladder, bacteria are often eliminated by voiding or by the immune system. If this does not occur asymptomatic bacteriuria may result,[1] i.e. the presence of a significant growth of bacteria in the urine with no urinary symptoms. Alternatively, a symptomatic urinary tract infection (UTI) may result (see: "Why do some bacteria cause symptomatic infections?", over page). Bacteria may also gain access to the urinary tract via the circulatory system. This is, however, a relatively rare cause of bacteriuria.[1]

In general the prevalence of asymptomatic bacteriuria increases in both older males and females, although it is more prevalent in females of all ages.[2] Approximately 20% of females and 5 – 10% of males aged over 80 years have asymptomatic bacteriuria,[3] and the prevalence may be as high as 50% in older females in residential care facilities.[4] Females are more susceptible to bacteriuria because of the reduced distance between the urethra and the anus and the reduced length of the urethra compared to males.

Asymptomatic bacteriuria is inevitable in all patients with long-term indwelling or supra-pubic catheters. Even when best-practice catheter insertion and care are followed, bacteriuria is reported to be acquired by catheterised patients at a rate of 2 – 7% per day,[2] and to occur in all catheterised patients within approximately four weeks.[4]

Asymptomatic bacteriuria in older patients does not need to be treated

It is rarely appropriate to treat asymptomatic bacteriuria in older patients with antibiotics. This is because asymptomatic bacteriuria is effectively harmless and needlessly treating patients with antibiotics exposes them to an increased risk of antibiotic-associated adverse effects, e.g. diarrhoea, nausea and potential allergic reaction. Inappropriate prescribing of antibiotics to treat older patients with asymptomatic bacteriuria also selects for bacteria that are antibiotic resistant. This increases the risk of a patient subsequently developing a symptomatic infection from a strain of bacteria that is resistant to treatment. In a residential care facility this can be particularly problematic as it increases the risk of an outbreak of antibiotic-resistant infections. Furthermore, in some people the normal microflora of the urinary tract is protective against the development of symptomatic UTIs.[2, 4] Therefore disrupting the natural growth of microorganisms in the urinary tract with unneeded antibiotics further increases a patient's risk of developing a symptomatic UTI in the future.[4]

Studies in many different groups of patients have consistently demonstrated that the treatment of asymptomatic bacteriuria with antibiotics is associated with increased adverse outcomes and is at best a needless waste of resources.[5] This is even true in people who are immunosuppressed. In a study of 260 females with autoimmune rheumatic disease and a mean age of 52, the majority of whom were taking immunosuppressive medicines, the presence of asymptomatic bacteriuria was not associated with a significantly increased risk of developing UTIs over a one-year follow-up period.[6]

Do not request urine culture in older patients who are asymptomatic

Do not request urine culture in older patients who do not have symptoms of a urinary tract infection (UTI). Routine urine dipstick in older people solely for the purposes of detecting bacteriuria is unlikely to be helpful in patients without urinary symptoms and should also be avoided.

Is testing for asymptomatic bacteriuria ever appropriate?

In theory a finding of asymptomatic bacteriuria in an older patient should be uncommon as laboratory testing for bacteriuria in patients without urinary symptoms is not recommended. One situation where it is appropriate that a urine sample be taken for culture is prior to procedures that involve entering the urinary tract and breaching the mucosa, e.g. endoscopic urological surgery.[4] Testing for, and treatment of, bacteriuria prior to major joint surgery is often requested by clinicians in secondary care, although it is of uncertain benefit.[7]

N.B. In contrast to the situation in older patients, treatment of asymptomatic bacteriuria in pregnant women is recommended as it is associated with an increased risk of symptomatic UTI, including pyelonephritis.[4]

Investigating and managing cystitis in older people

In general UTIs in older patients are more difficult to diagnose and more difficult to manage than in younger populations. Most of the guidance on UTI investigation and management relates to younger female populations and in older populations a flexible approach is required that takes into account individual factors and patient circumstances. Older females experience cystitis, i.e. a lower UTI, more often than older males, although the difference in prevalence between females and males is less than in younger age groups.[3]

Diagnosing cystitis in older females and males

The classical symptoms and signs of cystitis are similar in older females and males, and include:[2]

- Dysuria
- Frequency
- Suprapubic tenderness
- Urgency
- Polyuria
- Haematuria

Why do some bacteria cause symptomatic infections?

It is thought that not all bacteria are capable of inducing symptomatic UTIs.[4] Some strains of bacteria within a species are uniquely equipped with virulence factors, e.g. specialised pili (appendages resembling hair), and are more readily able to ascend from the faecal flora, introitus vaginae or periurethral area and into the bladder, and less frequently to the kidneys.[4] The more the natural defences of the person are compromised, e.g. by obstruction or bladder catheterisation, the less virulent the bacteria needs to be to cause symptomatic infection.[4] *E. coli* are reported to account for 80–90% of lower UTIs.[8]

A person's genetics, the presence of any underlying conditions, e.g. diabetes, and lifestyle factors influence the likelihood of them developing a UTI.[1]

Table 1: Recommendations for urinary investigation in patients aged 65 years and over with symptoms and signs suggestive of urinary tract infection (UTI)

Patient catheterisation	Patient sex and presentation	Recommendation on urinary testing
Uncatheterised	Females with symptoms of uncomplicated cystitis, e.g. no recent history of UTIs and without co-morbidities	Urine dipstick and culture is not routinely required as a diagnosis can generally be made on symptoms and signs alone and empiric treatment with trimethoprim or nitrofurantoin given for three days.
	Females with symptoms of complicated cystitis, e.g. recurrent UTIs	Urine culture is recommended in all female patients with complicated cystitis. Further investigation of the urinary tract may be necessary to exclude anterior vaginal prolapse,* e.g. cystocoele, and differential diagnoses such as atrophic vaginitis.
	Females and males with symptoms of pyelonephritis	Urine culture is recommended in all females and males with a suspected pyelonephritis. Empiric treatment can be initiated with co-trimoxazole for 10 days. Further investigations may be appropriate in some patients to exclude the possibility of an underlying obstructive cause.
	Males with symptoms of cystitis	Urine culture is recommended in all males with a suspected UTI and therefore dipstick testing is of limited benefit. However, a positive dipstick result for leukocyte esterase or nitrites can help "rule in" a UTI, but negative results should not be used to "rule out" a UTI. Empiric treatment can be initiated with either trimethoprim or nitrofurantoin for seven days.
Catheterised	Males or females	All patients with long-term catheters can be expected to have bacteriuria and pyuria, therefore urine dipstick testing for leukocyte esterase or nitrites is not helpful. Equally, the presence of bacteriuria on culture is unlikely to be useful diagnostically and urine culture is recommended only to confirm bacteriuria and guide antibiotic treatment.

* Anterior vaginal prolapse may cause retention of small amounts of urine after voiding and increase the risk of a symptomatic UTI

The symptoms of UTIs may be difficult to differentiate from chronic genitourinary symptoms that are more common in older patients, including worsening urgency, incontinence, dysuria as well as non-specific symptoms such as anorexia, fatigue, malaise and weakness.[9] Communication can also be an issue with older patients with dementia who may struggle to articulate their symptoms to health professionals.

The onset of symptoms can be helpful in differentiating symptomatic UTIs and long-term genitourinary problems, e.g. incontinence. New-onset dysuria in an older patient is the symptom with the strongest predictive value of UTI as it is not usually associated with urinary incontinence.[9] New-onset urgency and new-onset frequency are also associated with symptomatic UTIs, but these symptoms may also occur with worsening urinary incontinence.[9]

Dysuria, fever and age over 60 years are reported to be the strongest predictors of UTI in older males. In a sample of over 600 males in general practice with a median age of 65 years the predictive value when dysuria, fever and age over 60 years were all present was 92%.[10]

UTIs in older patients are more likely to be complicated

A UTI is considered to be complicated if the patient has an abnormality of the genitourinary tract or an underlying condition that makes them less likely to respond to standard treatment or more likely to experience a severe outcome. Complicated UTIs are often recurrent, i.e. ≥ three UTIs in 12 months,[11] because the underlying abnormality or condition predisposes the patient to repeat infection.[12] An older female patient with recurrent UTIs is likely to have a complicated UTI because genitourinary abnormalities which increase urinary retention are more common in older patients (see below). It is important that any underlying genitourinary condition that predisposes a patient to UTIs is managed appropriately. At least half of patients who present with a UTI due to an untreated genitourinary abnormality can be expected to experience a recurrent UTI within six weeks of completing a course of antibiotics.[12]

All UTIs in males are considered to be complicated because they are associated with structural abnormalities in the urinary tract, e.g. inflammation or obstruction due to benign prostatic enlargement, strictures, renal stones or malignancy.[2, 13]

Risk factors that increase the likelihood of a complicated UTI in older females include:[4, 12]

- Recurrent UTIs
- Previous genitourinary surgery
- Urinary incontinence
- Bladder diverticula
- Atrophic vaginitis due to oestrogen deficiency
- Anterior vaginal prolapse, e.g. cystocoele
- Urinary catheterisation
- Uncontrolled diabetes
- Recent overseas travel (due to atypical bacteria)
- A general decline in health in a patient in residential care

For further information on managing patients with suspected renal stones, see: "Managing patients with renal colic in primary care: know when to hold them", (BPJ 60, Apr 2014).

Complicated UTIs are caused by a more diverse array of bacteria

The majority of uncomplicated cystitis in older people is caused by *E. coli*, and while this is also the predominant organism in complicated cases, other species of bacteria may be involved, e.g. *Klebsiella pneumoniae*, *Citrobacter spp*, *Serratia spp*, *Enterobacter spp* or *Pseudomonas aeruginosa*.[4] Multi-drug resistant organisms are more prevalent in patients with complicated UTIs because the patient is more likely to have been exposed to multiple courses of antibiotics to treat previous infections caused by an underlying genitourinary condition.[4]

Urine dipstick is not necessary for diagnosing UTIs

Urine dipstick is not required for the diagnosis of cystitis in females or males but it is helpful in some situations. Urine dipstick is of most use in "ruling out" a diagnosis of a lower UTI in an older patient with non-specific symptoms, such as confusion, in the absence of classical symptoms, e.g. dysuria.[9]

In a patient with symptoms of cystitis a urine dipstick positive for nitrites increases the likelihood that the patient has a UTI.[1] However, because only Enterobacteriaceae are able to metabolise nitrates to nitrites a negative urine dipstick does

not exclude the possibility of a UTI caused by another species of bacteria. The level of nitrites must reach a threshold for detection and therefore a patient with a UTI who is drinking lots of water and voiding frequently is more likely to test negative for nitrites on dipstick.[1] A systematic review of 16 studies including over 3 700 patients found that the presence of dysuria alone had a probability of 62% of predicting significant bacterial counts on urine culture; when this was combined with a positive result for nitrites this increased to 88%, and decreased to 47% when combined with a negative result for nitrites.[14]

A urine dipstick test positive for leukocyte esterase is reported to have 75 – 96% sensitivity for pyuria and 94 – 98% specificity.[15] However, pyuria itself is not specific for UTIs and pyuria without bacteriuria may occur in patients with urinary catheters, renal stones or inflammatory conditions of the genitourinary tract, e.g. bladder pain syndrome (also known as interstitial cystitis).[4, 15]

Haematuria on dipstick in a symptomatic patient who also has pyuria and nitrites may also be consistent with a UTI, but the possibility of malignancy should always be considered when interpreting a finding of haematuria.[1]

Request urine culture to confirm bacteriuria and establish susceptibility

Urine culture is not primarily a tool for the diagnosis of UTIs, as this is largely done on the basis of the patient's symptoms and signs.[2]

The main value of urine culture is to inform management of patients with UTIs by confirming the presence of significant bacteriuria and reporting on bacterial susceptibility to antibiotics.[2] Urine culture is not necessary in older female patients with classical symptoms of uncomplicated cystitis, who can be treated empirically. **Urine culture should be requested for older female patients with**: recurrent cystitis, persistent urinary symptoms following empiric antibiotic treatment, or atypical symptoms to exclude the possibility of a UTI, e.g. nausea, vomiting, confusion or abdominal tenderness. **Urine culture should be requested for all males with suspected cystitis**.

Pyuria on microscopy can be expected to be found in virtually all older patients with cystitis.[1] Bacteriuria without pyuria is consistent with contamination or colonisation, while pyuria or haematuria without bacteriuria is suggestive of other conditions, e.g. nongonococcal urethritis, urinary stones or malignancy in older males.

Urine samples should be stored at approximately 4°C until they are sent to the laboratory as bacteria will continue to multiply in samples stored at room temperature which will lead to inaccurate colony counts. In New Zealand, 100×10^6 colony forming units (CFUs) of bacteria per litre of voided urine is the cut-off distinguishing clinically significant bacteriuria from contamination; the presence of urinary symptoms then determines whether the diagnosis is asymptomatic bacteriuria or UTI.

N.B. When a urine sample is sent for culture the laboratory will first perform microscopy and then urine culture if the microscopy is suggestive of bacteriuria. Susceptibility testing is then performed on all urine samples that are cultured. General practitioners are also able to specify that urine culture be performed regardless of the results of urine microscopy. In this article the term "urine culture" refers to urine microscopy, culture and susceptibility testing.

General practitioners are encouraged to include clinical information on urine testing request forms, rather than, for example "?UTI". This includes the type of specimen that has been collected, e.g. MSU or catheter, and the presence of relevant symptoms and signs. This information will improve the laboratory's interpretation of the results and alter how the results are reported. For example, urine samples taken from catheterised patients (see: "Collecting urine for culture", over page) are less likely to be contaminated by periurethral flora and therefore lower colony counts may represent significant bacteriuria. Additionally, a low colony count may be significant in a MSU sample from an older female patient without a history of UTIs who is otherwise healthy but has symptoms of dysuria and frequency.

All older males with cystitis require further investigation

Lower urinary tract symptoms in older males may be caused by benign prostatic hyperplasia or related to previous procedures such as transurethral resection of the prostate.[4] Chronic bacterial prostatitis is reported to be the most frequent cause of recurrent UTI in males.[4] Symptoms of prostatitis include: dysuria, frequency and pain in the prostatic, pelvic or perianal area.[1] However, patients with chronic bacterial prostatitis may not appear to be unwell and on examination the prostate may feel normal, tender or boggy.[13] A urinary tract ultrasound should also be considered and may form the basis of a discussion with, or referral to, an urologist.

Managing cystitis in older females and males

Managing older patients with UTIs often requires additional considerations, compared with younger patients, as they are more likely to have significant co-morbidities, e.g. long-term or less well-controlled diabetes, or be living in residential care where the prevalence of antibiotic resistant UTIs is higher (see: "Managing UTIs in older patients with diabetes", opposite, and "Managing UTIs in patients living in residential care", Page 22).

The choice of empiric antibiotic for the treatment of cystitis in females and males is the same, except that males require a longer, seven day, regimen compared to three days in females. New Zealand-based and international guidelines recommend that all non-pregnant females and males with acute cystitis be treated with a course of trimethoprim or nitrofurantoin:[2, 18, 19, 20]

- Trimethoprim, 300 mg, once daily at night (for three days for females and seven days for males) **or**
- Nitrofurantoin, 50 mg, four times daily* (for five days for females and seven days for males); avoid in patients with creatinine clearance < 60 mL/min

* Four times daily dosing of nitrofurantoin 50 mg is required to achieve optimal therapeutic concentrations over a 24 hour period. Nitrofurantoin is available in a 100 mg sustained-release formulation overseas which is taken twice-daily, but the nitrofurantoin 100 mg formulation available in New Zealand is not sustained-release and should not be taken twice daily by patients with UTIs.

Norfloxacin, 400 mg, twice daily (for three days for females and seven days for males), is an alternative treatment for UTIs but is reserved only for patients with isolates that are resistant to trimethoprim or nitrofurantoin.[20]

Females with complicated cystitis require longer treatment regimens than females with uncomplicated cystitis and this may range from 7 – 21 days depending on the clinical situation, including whether an underlying genitourinary condition is being treated concurrently.[4]

Ciprofloxacin, 500 mg, twice daily, for 28 days is indicated for the treatment of acute or chronic prostatitis as this class of medicine has excellent penetration into the prostate.[4, 9] Ciprofloxacin is not recommended for treating males or females with uncomplicated cystitis.

Investigating and managing pyelonephritis in older people

Male and female patients with symptoms of pyelonephritis, i.e. an upper UTI, are generally diagnosed and managed in the same way.

Collecting urine for culture in symptomatic patients

Midstream urine collection is recommended when sampling urine for dipstick or laboratory analysis.[4] Cleansing of the external genitalia is not necessary when collecting urine as there is no evidence that this reduces contamination.[16]

When taking a urine sample from a catheterised patient, if it is a short-term catheter, e.g. has been in place for less than a week, then the urine sample can be taken through the catheter port using aseptic technique.[17] If the patient has a long-term indwelling urinary catheter then ideally it is recommended that a urine sample be taken immediately after a fresh catheter is inserted into the patient.[17]

Symptoms of pyelonephritis

Symptoms and signs consistent with pyelonephritis include:[4]

- Flank pain
- Nausea and vomiting
- Fever > 38°C, sometimes with rigors
- Tenderness over the renal area

Pyelonephritis can occur with or without symptoms of cystitis.[4]

Investigating pyelonephritis in older females and males

Urine culture is recommended in all patients with suspected pyelonephritis (Table 1, Page 17).[4] An ultrasound of the renal tract may be considered to exclude the possibility of an obstruction and if a renal stone is suspected then a CT urogram should be requested.[4, 20] It is important to exclude the possibility of an obstruction early in a patient who is systemically unwell as urinary blockage can quickly lead to urosepsis.[4] Prostatitis should be considered in all older males with symptoms of pyelonephritis.[4]

Depending on the patient's age and renal function, urgent FBC, CRP, electrolytes and creatinine should also be considered.

Antibiotic treatment of pyelonephritis in older females and males

The recommended empiric oral antibiotic treatment for males or females with suspected pyelonephritis is:[20]

- Co-trimoxazole 160+800 mg (two tablets), twice daily, for ten days

Amoxicillin clavulanate is a second-line option (500+125 mg, three times daily, for ten days). Ciprofloxacin (500 mg, twice daily, for seven days) is a third-line option, but only for isolates resistant to initial empiric choices.[20]

Patients with severe pyelonephritis may not be able to take oral medicines due to nausea or vomiting and referral to hospital may be appropriate to initiate intravenous treatment, particularly in dehydrated patients with reduced renal function.[4] Patients treated in a hospital setting, might be given oral trimethoprim after IV antibiotic treatment, if the isolate is susceptible. Nitrofurantoin is not recommended for the treatment of pyelonephritis as it fails to achieve effective tissue penetration.[2]

Managing UTIs in older patients with diabetes

People with diabetes are more at risk of developing cystitis and pyelonephritis.[4] In an otherwise healthy older female patient with well-controlled diabetes an isolated diagnosis of cystitis may be considered uncomplicated.[4] However, patients with long-term or poorly-controlled diabetes are more likely to develop a neuropathic bladder with voiding abnormalities which may complicate the clinical picture.[4] Urine culture is recommended in all older patients with poorly-controlled diabetes and symptoms of a UTI and additional investigations, e.g. a urinary tract ultrasound, may be appropriate to assess the patient's residual urinary volume.

Patients with diabetes and pyelonephritis are at an increased risk of developing metabolic complications, e.g. hypo- or hyperglycaemia, hyperosmolar dehydration and ketoacidosis.[4] Some patients with diabetes and pyelonephritis require close observation and blood glucose monitoring depending on the severity of their condition. Referral to hospital may be appropriate to initiate intravenous treatment, particularly in dehydrated patients with diabetes and reduced renal function.

Managing UTIs in patients living in residential care

Residential care facilities can be reservoirs of multi-drug resistant organisms and inappropriate treatment of asymptomatic bacteriuria contributes to this problem.[21] Bacteria causing UTIs may display increased resistance to nitrofurantoin, ciprofloxacin and cephazolin.[21] In a study of 76 older patients in South Canterbury with a urine sample positive for multi-drug resistant *E. coli*, the factors which conferred the greatest risk of developing a multi-drug resistant UTI were living in a residential care facility and previous antibiotic treatment while in hospital, for any reason.[21] A general deterioration in health and functional status is a further risk factor for the development of complicated UTIs in patients in residential care facilities.[4] Urine culture is recommended in all patients living in residential care facilities who are suspected of having a UTI to improve antibiotic selection and reduce the spread of multi-drug resistant organisms. If susceptibility testing indicates resistance to commonly available antibiotics, or the patient is intolerant to antibiotics that are available, discussion with a clinical microbiologist is recommended. Alternative, unapproved, antimicrobial medicines, e.g. pivmecillinam hydrochloride or fosfomycin, are now being used in some DHBs for the treatment of cystitis.

Investigating and managing catheter-associated UTIs in older people

One of the most important risk factors for developing a catheter-associated UTI is the length of time that the patient has been catheterised. Therefore minimising the length of time that a patient has a urinary catheter in place reduces their risk of developing a UTI.

The diagnosis and management of catheter-associated UTIs is generally the same in females and males. The virtually constant presence of bacteriuria and pyuria in catheterised patients can make the diagnosis of a UTI difficult. Urine culture is therefore unlikely to be able to exclude a UTI and is more useful in determining antimicrobial susceptibility to guide antibiotic treatment.

Symptoms and signs of catheter-associated UTIs in females and males

There is no specific constellation of symptoms or clinical signs that characterise UTIs in catheterised patients.[2] The symptoms of UTI in catheterised patients may also be general and not localised to the urinary tract, including:[2]

- New or worsening fever
- Rigors
- Altered mental status
- Malaise or lethargy with no identified cause
- Flank pain
- Acute haematuria
- Pelvic discomfort

Investigating and treating UTIs in catheterised patients

Patients with long-term urinary catheters are more likely to present with polymicrobial UTIs,[17] therefore urine culture is essential in all long-term and recently catheterised patients with a suspected UTI to guide antibiotic treatment (Table 1, Page 17). If a patient develops a UTI within 48 hours of urinary catheter removal then urine culture should also be requested.[17]

If a catheterised patient is febrile, blood cultures are recommended to assess for systemic involvement before beginning antibiotic treatment.[4] However, the decision to treat a UTI in a catheterised patient should not be made on the presence of fever alone; only approximately one-third of cases of fever in catheterised patients are caused by UTIs and

other possible causes should be ruled-out before antibiotics are prescribed for the treatment of UTI.[2, 4]

Once antibiotic treatment for a UTI is started in a patient with a urinary catheter the catheter should be changed as bacteria adhering to it will not be eliminated by the antibiotic. Referral to hospital should be considered for patients with a UTI who are living in the community and are unable to tolerate oral medicines due to nausea or vomiting, particularly if they develop signs of systemic involvement, such as fever, rigors or confusion.[2]

Follow-up of older people treated for symptomatic UTIs

If the patient's symptoms resolve then it can generally be assumed that the UTI has resolved.[9] In patients whose urinary symptoms have resolved a "test for cure" is not recommended as the presence of asymptomatic bacteriuria that has either persisted or developed recently may be misinterpreted.[9] In other words, the patient may have been "cured" but a finding of asymptomatic bacteriuria might lead a clinician to believe that treatment had not been successful.

If a patient's symptoms have not resolved by the time they have completed an empiric antibiotic regimen or their symptoms return shortly after finishing treatment, e.g. within two weeks, then urine culture and susceptibility testing is recommended to select an antibiotic with more appropriate coverage; the laboratory should be informed as to what antibiotic the patient had been previously prescribed.[4] If haematuria persists following resolution of a UTI then further investigation or referral to an urologist is appropriate.

Managing recurrent UTIs in older female patients

A history of recurrent UTIs in an older female suggests an underlying cause that has not been identified or effectively managed. In older female patients consider if urinary incontinence or urine retention may be a predisposing factor for recurrent UTIs. Intermittent catheterisation is a potential treatment for incomplete voiding.

Reconsider if the diagnosis is correct

There are a number of other conditions that are more prevalent in older females that can cause vulvovaginal symptoms similar to UTIs. A specific description of the patient's symptoms along with an examination of the vulvovaginal area will usually help to exclude the possibility of these conditions.

Atrophic vaginitis can cause vaginal discomfort and urinary incontinence in older females.[22] Vaginitis due to vaginal atrophy following a reduction in ovarian oestrogen secretion also increases the likelihood of an older female developing cystitis. Oestrogen cream stimulates lactobacillus in the vaginal epithelium and reduces the pH of the microenvironment thereby reducing the likelihood of vaginal colonisation by Enterobacteriaceae.[22] Ovestin cream (0.1%) is indicated for menopausal atrophy of the lower urogenital tract.[19] In older females with recurrent UTIs periurethal application of ovestin cream, with or without intravaginal application depending on the severity of any atrophic vaginitis, can be considered.

For further information on other potential differential diagnoses, see: "Vulvovaginal health in post-menopausal women", BPJ 63 (Sep, 2014).

Non-pharmacological interventions for the prevention of recurrent UTIs

Studies have failed to demonstrate a reduction in UTI risk through behavioural interventions such as increasing fluid consumption, wiping from front to back following defaecation and avoiding occlusive underwear.[4] However, discussing these factors with the patient may be useful in emphasising the importance of good hygiene practices in general.

Cranberry products, e.g. juice or concentrated capsules, are often recommended to reduce the incidence of recurrent UTIs.[4] However, a 2012 Cochrane review found that cranberry juice was less effective than had been previously thought and that it could not be recommended for the prevention of UTIs.[23] This review also highlighted the difficulty of knowing if there was a sufficient quantity of "active" ingredient in concentrated preparations of cranberry extract.[23] International guidelines do not make recommendations for or against the consumption of cranberry products for the prevention of recurrent UTIs.[4] A pragmatic approach would be to suggest that the patient trials the daily use of cranberry capsules but to monitor the frequency of urinary symptoms and to cease the supplement if the frequency of UTIs does not decrease.

There is some weak evidence that ascorbic acid (vitamin C) supplementation, 100 mg daily, may reduce the risk of recurrent UTIs in younger females.[24] However, there is no evidence that this is effective in older females. Bicarbonate + citric acid + tartaric acid powder (Ural) is indicated and subsidised for the relief of discomfort in patients with UTIs, but there is no evidence that this reduces the prevalence of UTIs.

Lactobacillus containing probiotics have not been widely studied in their effectiveness at preventing recurrent UTIs. Vaginal application of products containing *Lactobacillus crispatus* may reduce the rate of recurrent UTIs in younger females, but oral lactobacilli has not been demonstrated to do so.[4] There is currently no evidence available suggesting that probiotics are effective at preventing UTIs in older people and guidelines recommend that they are not used for this purpose outside of clinical trials.[4]

Prophylactic antibiotics are a last-line treatment option

Prophylactic antibiotics should only be considered in primary care as a treatment of last resort for the prevention of recurrent UTIs in older people. If prophylactic treatment is initiated the choice of antibiotic should be based on the identification and susceptibility testing of the organism causing the UTIs along with any patient history of antibiotic intolerance or adverse drug reactions; discussion with a clinical microbiologist is likely to be helpful.[4] Nitrofurantoin, 50 or 100 mg, once daily, continuously, is a possible regimen for older females with recurrent UTIs.[4] Nitrofurantoin should be avoided in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2 and its use is associated with the development of interstitial lung disease and pulmonary fibrosis,[19] particularly in elderly people and with longer courses;[2] ask patients regularly about any respiratory symptoms, e.g. cough or shortness in breath, and advise them to report any new difficulties in breathing promptly. Prophylactic antibiotics should be stopped if there is no decrease in the rate of UTIs.

It is recommended that the use of prophylactic antibiotics in patients with urinary catheters generally be avoided.[2, 4] Prophylactic antibiotics do not appear to reduce the incidence of symptomatic UTIs in patients with short-term urinary catheters and there is a insufficient evidence available to recommend their use in patients with long-term catheters.[4] Rarely, it may be appropriate to consider the use of prophylactic antibiotics in catheterised patients whose quality of life is reduced by either the frequency or severity of recurrent UTIs, or in patients with a history of UTIs following catheter change.[2]

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