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Serum protein bands

Lab tests during pregnancy

Quiz feedback: Thrombophilia, CRP, fungal infections

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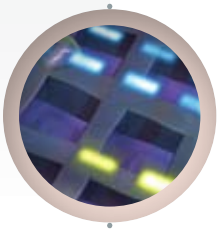

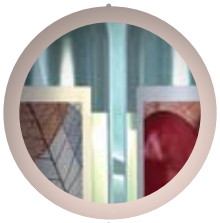

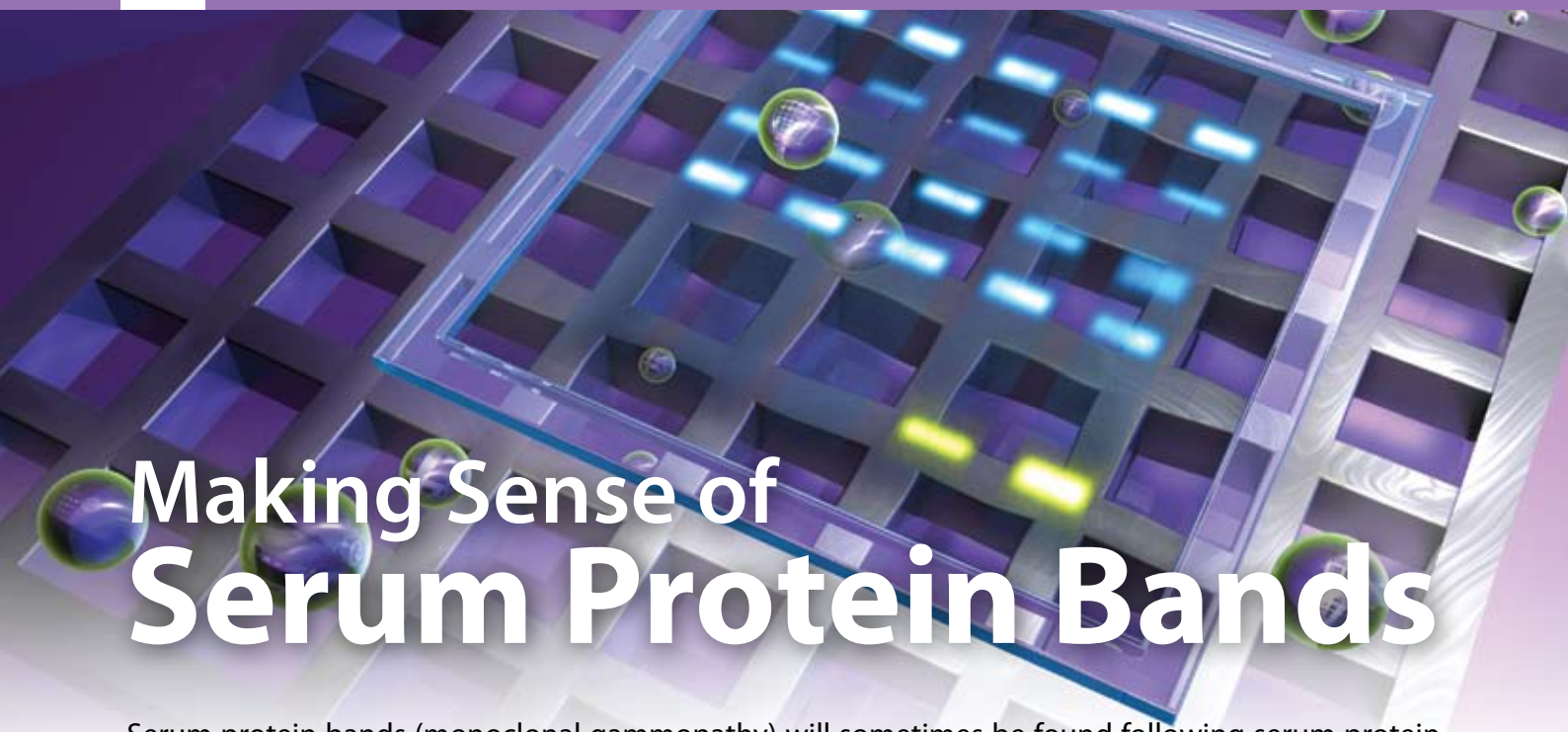

Making Sense of Serum Protein Bands

Serum protein bands (monoclonal gammopathy) will sometimes be found following serum protein electrophoresis in patients presenting with classic signs or symptoms of multiple myeloma, e.g. bone pain. In other cases, patients may have non-specific symptoms, meaning the discovery is more unexpected. Irrespective of how the band is discovered, there are additional tests that can be performed to provide more information to help with the diagnosis and to guide management. These tests include; immunofixation, Bence-Jones protein and serum free light chains.

While we may recognise the names of some of the tests, it can be confusing to know the situations in which they should be requested, and even what the results mean. This article provides an overview of the clinical situations in which a patient may have a monoclonal gammopathy in their serum, what these results mean, and the role of other related laboratory tests.

In a general practice setting, test results showing increased protein in serum or urine are often incidental findings when investigations have been requested for other reasons. Patients with clinical conditions such as multiple myeloma, that increase the levels of protein in serum or urine, may present with a wide range of symptoms or may be asymptomatic. In these patients serum protein electrophoresis may have been requested as part of the initial work-up.

Levels of protein in the serum change in a predictable way in response to many clinical conditions, such as inflammation, trauma (including burns and chemical injury), malignancy, infarction and necrosis.[1] Serum protein electrophoresis is a laboratory test used to help identify patients with multiple myeloma and other serum protein disorders, by separating serum proteins into their various components. Indications for serum protein electrophoresis are numerous and are based on clinical, laboratory and occasionally radiological findings (see "Indications for requesting serum protein electrophoresis").

Electrophoresis fractions

Serum protein electrophoresis separates serum proteins into the following fractions: albumin, alpha, beta and gamma globulins. Approximately 60% of the total protein in the serum is albumin, while the remaining fractions are composed mainly of globulins, predominantly immunoglobulins. The gamma fraction contains the largest portion of immunoglobulins, hence an increase in gamma globulin is referred to as a gammopathy.

Gammopathies can be either polyclonal, characterised by a broad diffuse band in the electrophoresis pattern, or monoclonal where the band is sharp and well defined. Making the distinction between a monoclonal and polyclonal gammopathy is important.

Monoclonal gammopathies are associated with excessive production of immunoglobulins from a single clone of cells that is malignant or potentially malignant, whereas polyclonal gammopathies are characterised by a generalised increase in immunoglobulins.[1] A polyclonal gammopathy can be caused by various infections, haematologic diseases, liver disease, some malignancies and inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, temporal arteritis and sarcoidosis.

This article focuses on monoclonal gammopathies, and provides guidance on the laboratory management of conditions associated with these.

What is a monoclonal gammopathy?

Various terms are used to describe a monoclonal gammopathy, which can be confusing. The following names are frequently used:

- Monoclonal protein
- Paraprotein
- M-protein/band/spike
- Monoclonal gammopathy

Monoclonal gammopathy

Monoclonal gammopathy is the name given to a "band" in serum protein electrophoresis, caused by the overproduction of a population of plasma cells, which in turn produce a single immunoglobulin (the so-called "plasma cell dyscrasias"). As there is a finite capacity in the bone marrow, an enlarging clone of plasma cells expands at the expense of other cells. Levels of other normal immunoglobulins eventually fall, referred to as immune paresis. While this is most often associated with multiple myeloma, it is quite frequently an unexpected discovery, and may be related to a number of conditions.

Indications for requesting serum protein electrophoresis[1,2,3]

Indications based on clinical findings:

- Suspected multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis or other related disorders
- Unexplained bone pain or fracture
- Recurrent infections
- Unexplained peripheral neuropathy (not able to be attributed to another condition, e.g. type 2 diabetes, chemotherapy)

Indications based on laboratory findings:

- High (or low) total serum globulin or immunoglobulin
- Extremely high percentage of lymphocytes
- Incidental finding of an increased total protein level
- Unexplained anaemia (multiple myeloma is a recognised cause of non-iron deficiency anaemia) or other persisting cytopaenias for which there is no other explanation
- Unexplained high ESR (>50) with a normal CRP
- Unexplained hypercalcaemia or renal impairment
- Red cell rouleaux formations noted on the peripheral blood smear
- Unexplained high urine protein with relatively low or normal urine albumin
- Presence of urine free light chains (Bence-Jones proteinuria)

Indications based on radiological findings:

- Lytic lesions in bone
- Unexplained osteopaenia (as not all patients with multiple myeloma will have osteolytic lesions)

Conditions associated with monoclonal gammopathy

There are a number of conditions associated with monoclonal gammopathy. In the first instance, most GPs will think of multiple myeloma, but this is less common, and most people will be found to have a monoclonal gammopathy of undetermined significance (MGUS). Table 1 compares the incidence of these conditions.

Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is the most common monoclonal gammopathy. It describes the presence of a monoclonal protein without sufficient clinical or laboratory evidence to diagnose one of the other associated conditions. It is the most frequent diagnosis of a monoclonal gammopathy, and has an incidence approximately 60 times greater than multiple myeloma (1% in people aged over 50 years, rising to up to 8% of people aged over 70 years).[4, 5]

Approximately 1% of patients per year with MGUS will progress to multiple myeloma, therefore periodic (usually annual) monitoring should be done (with serum protein electrophoresis, immunoglobulins and complete blood count). There is no plateau time, beyond which development of a condition such as multiple myeloma will not occur. However, reactive bands, which can occur as part of the immune response to an inflammatory stimulus, often reduce or disappear when followed.

Multiple myeloma

Multiple myeloma is uncommon and has an incidence of approximately 40 per million people. It is rare under the age 40 years, but its incidence rises to over 300 per million in people aged over 80 years. The median age at diagnosis is 69 years with a slight male predominance.[3]

Patients with multiple myeloma can be classified as having asymptomatic (formerly known as smouldering) or symptomatic (active) disease.

Anaemia and bone marrow failure, infections, renal impairment, bone pain and pathological fractures are common clinical features. The differential diagnosis of multiple myeloma is shown in Table 2.

Less common associations of monoclonal gammopathies

Lymphomas: monoclonal gammopathy is a common feature of primary lymphoproliferative conditions such as chronic lymphocytic lymphoma.

Waldenström's macroglobulinaemia: a type of small cell lymphoma associated with production (often large amounts) of monoclonal IgM. The median age at presentation is 63 years, and over 60% of patients are male. Clinical features include enlargement of liver and spleen and anaemia, due to increasing concentration of IgM, and hyperviscosity syndrome.[3]

Table 1: Conditions with monoclonal gammopathies[6, 7, 8]

Condition	Clinical Effect	Incidence
Monoclonal gammopathy of undetermined significance (MGUS)	Asymptomatic with risk of progression	1% >50 years, rising up to 8% >70 years
Multiple myeloma	Severe	40 per million, but increases to 300 per million for people >80 years
Waldenström's macroglobulinaemia	Moderate	0.1 per million at age <45 years and 36.3 per million at age >75 years.
Amyloidosis	Severe	8 per million

Table 2: Differential diagnosis of multiple myeloma (adapted from O'Connell, et al 2005)[1]

Disease	Distinctive features
Multiple myeloma (active)	Monoclonal gammopathy in serum or urine – plasma concentration >30 g/L (IgG or A) or lower concentration of monoclonal IgD or light chain band ***and*** ≥10% plasma cells in bone marrow ***and*** evidence of organ dysfunction involving one or more of: lytic bone lesions or osteoporosis, anaemia, hypercalcaemia or renal disease
Asymptomatic myeloma (smouldering)	Monoclonal gammopathy ≥30 g/L (IgG) and/or ≥10% plasma cells in bone marrow ***but*** no evidence of disease-specific end-organ damage – no lytic bone lesions, anaemia, hypercalcaemia or renal disease
Monoclonal gammopathy of undetermined significance	Monoclonal gammopathy <30 g/L and <10% plasma cell in bone marrow ***and*** no evidence of disease-specific end-organ damage – no lytic lesions, anaemia, hypercalcaemia or renal disease
Waldenström's macroglobulinaemia	IgM monoclonal gammopathy, and ≥10% bone marrow infiltration with lymphoplasmacytic cells (with characteristic immune phenotype) Clinical features include hyperviscosity, anaemia, and enlargement of liver, spleen and lymph nodes

Amyloidosis: Primary amyloidosis is associated with a monoclonal gammopathy in 85% of cases and is characterised by pathological deposits of monoclonal light-chain fragments in various tissues such as heart, liver, bone marrow, lymph nodes and bowel.

Plasmacytoma: refers to a localised solid collection of plasma cells in the body outside the bone marrow.

Laboratory tests for monoclonal gammopathies

There are number of laboratory tests which are useful for determining the presence of a monoclonal gammopathy, and then eventually characterising it.

Serum total protein and albumin

These are relatively crude tests, but will often be abnormal if a monoclonal gammopathy and/or immune paresis is present. A large band may show as a high serum total protein with a raised calculated globulin result. If the total serum protein is very high, e.g. >90 g/L, protein electrophoresis may be performed on a reflex basis by the laboratory.

Immunoglobulins

A person with a monoclonal gammopathy will have an increase in a particular class of immunoglobulin: IgG, IgA, IgM or IgD (IgE monoclonal gammopathy is extremely rare). Quantitation of immunoglobulins (routinely IgG, IgA and IgM) is performed if a new monoclonal gammopathy is detected. It is also usually performed when following a known monoclonal gammopathy, to provide information about progression.

Serum protein electrophoresis

Serum protein electrophoresis is a means of separating serum proteins. A small amount of serum is placed on a specific medium (such as agarose) and an electrical charge is applied. The proteins then migrate across the medium in a characteristic manner, due to the net charge and size and shape of the protein.

In routine serum protein electrophoresis, the protein will separate into five main components (Figure 1), identified as albumin and the globulins (alpha1, alpha2, beta and gamma) . The gamma region contains the largest portion of globulins, therefore monoclonal gammopathies are most frequently encountered in this portion of the electrophoresis.

Immunofixation

When serum protein electrophoresis identifies a monoclonal gammopathy, the laboratory will automatically perform immunofixation (i.e. reflex test) to further determine the exact type of monoclonal protein. The heavy chain of the immunoglobulin will be identified as IgA, IgG or IgM (most commonly) or IgD (or IgE rarely). The light chains will be identified as kappa or lambda (κ or λ). In a minority of cases only light chains (without heavy chains) are produced. Light chain-only monoclonal gammopathy are often barely visible in serum but may show as large amounts of monoclonal light chains excreted in the urine; hence the need to consider urine testing when clearly suspecting a monoclonal gammopathy.

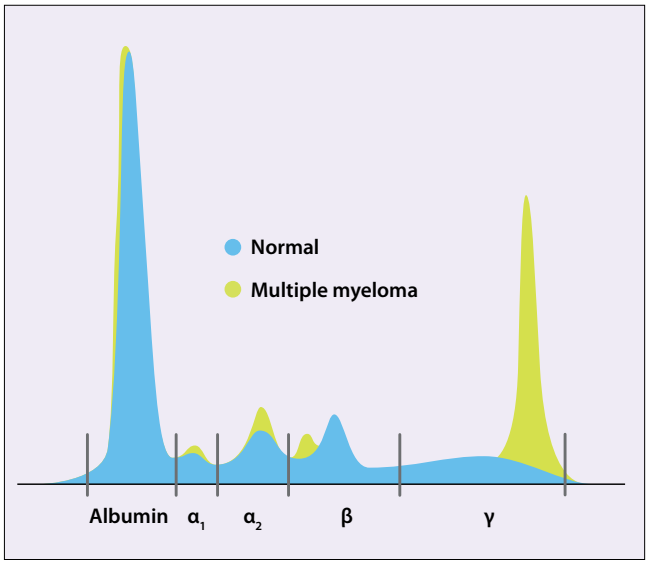

Figure 1: Serum protein electrophoresis

Urine free light chain testing (Bence-Jones protein)

Even in disease-free people, light chains are produced in small excess over heavy chains, creating a surplus of (polyclonal) free light chains. In a person with a monoclonal gammopathy this is often more marked, due to dysregulation of light versus heavy chain production. All of the excess light chains also have an identical class and mobility. Excess free light chains are frequently detectable in the urine by electrophoresis and immunofixation. The presence of monoclonal urine light chains, often referred to as Bence-Jones protein, is found nearly exclusively in patients with lymphoproliferative processes such as multiple myeloma.

Serum free light chains

Serum free light chain assays can detect normal levels of light chains in the blood, as well as elevated levels, even when those levels are undetectable by serum protein electrophoresis and immunofixation. Both free κ and λ chains are measured and the ratio is calculated. Excessive free κ or λ increases the likelihood a of monoclonal plasma cell disorder.

Some evidence suggests that in patients with newly identified MGUS, an abnormal light chain ratio increases the likelihood of progression independent of other factors such as band size and type. However, formal guidelines differ as to the use of serum free light chains in this setting. Recent British Haematology Society guidelines do not recommend their use, other than in patients who are otherwise at higher risk of progression (see "Monitoring monoclonal gammopathy") and those where a malignant plasma cell disorder is otherwise clearly suspected.

Serum free light chains are useful in certain specific and uncommon settings, e.g. concern over a possible non-secretory myeloma or amyloidosis, after specialist consultation. Light chains are sometimes used in specialist settings to monitor the response of mutiple myeloma to treatment.

Serum free light chains are not recommended as a first line routine test for plasma cell disorders. There is also no current evidence to support their use in long-term monitoring,[9] except for monitoring response of mutiple myeloma to treatment.

Clinical presentation of monoclonal gammopathy

Asymptomatic patients with chance findings

Approximately 30% of patients with monoclonal gammopathy are asymptomatic at diagnosis. In these cases the diagnosis is made due to an unusual result being noticed by either the laboratory or the GP. Some of the more suspicious laboratory findings include:

- Unexplained raised ESR (a monoclonal gammopathy does not increase CRP)
- Increased rouleaux formation on the blood film
- Increased serum total protein and/or calculated globulin (total protein minus albumin)
- Elevated immunoglobulin result

N.B. ESR and immunoglobulins are not recommended screening tests for monoclonal bands, which are only detected by electrophoresis

Symptomatic patients

Although the diagnosis of multiple myeloma is often made by chance, a significant number of people will present with symptoms.

Two-thirds of patients complain of bone pain, frequently located in the back, long bones, skull and pelvis. In addition, patients often have a range of non-specific (constitutional) symptoms, including fatigue, weight loss, chronic infections, paresthesia and symptoms related to hypercalcaemia.

As many patients with multiple myeloma present with lower back pain, a number of "red flags" have been identified in the assessment of patients with acute lower back pain. Multiple myeloma should be considered as a diagnosis in patients aged over 50 years with back pain persisting more than one month, if one or more red flags are identified (Table 3).

Testing for monoclonal gammopathy

In patients with a possible monoclonal gammopathy, the following investigations are required:

- Serum protein electrophoresis
- Urine free light chain testing

If a band is identified by serum electrophoresis or if immune paresis is noted then immunofixation, immunoglobulins and band quantification are recommended. A casual urine sample for protein and albumin and free light chains (Bence-Jones protein) should be collected. Other tests which should also be requested in this clinical situation are complete blood count, corrected calcium, creatinine (eGFR) and electrolyte measurements.

Monitoring monoclonal gammopathy

Periodic monitoring and watching for clinical and laboratory features of change is of key importance when managing patients with a monoclonal gammopathy. This is because transformation can occur, e.g. a patient may transition from MGUS to asymptomatic myeloma to multiple myeloma.

Approximately 1% of people with MGUS develop multiple myeloma, amyloidosis or Waldenström's macroglobinaemia annually, although most (especially those who are older at diagnosis) die of other diseases.[11]

The follow-up for patients with MGUS depends on the risk of progression. Both the British/Nordic Study Group

Table 3: Red flags for potential diagnosis of multiple myeloma in patients with back pain (adapted from George, et al 1991)[10]

Red Flags
Age over 50 years
Pain that is worse in supine position
Pain that is worse at night or awakens patient from sleep
Pain with a band-like distribution around the body
Pain that is not relieved with conventional methods (i.e., rest, nonsteroidal anti-inflammatory drugs)
Associated constitutional symptoms (fever, weight loss, dehydration)
Progressive neurologic deficit in lower extremities

(2009)[9] and the International Myeloma Working Group (IMWG, 2010)[12] have recently published guidelines. These differ in detail, but their common thread is that it is important to fully investigate patients at high risk, whereas those with low risk can be spared unnecessarily invasive initial investigations and need less frequent long-term monitoring.

The patient should be informed about the range of possible symptoms and advised to report new symptoms such as bone pain, weight loss, fatigue or other symptoms of progression. They should be aware that the risk of progression is life-long and does not plateau. The risk of eventual progression is higher for a young fit person with more years of life expectancy, than for an older person with other significant co-morbidities.

Low risk MGUS: The majority of patients with MGUS are at low risk of progression, judged by:

- Small band size (IgG <15 g/L OR IgA or IgM <10 g/L)
- They are asymptomatic
- No other abnormal results (normal adjusted calcium, creatinine and eGFR, blood count).

These patients should be followed-up several times in the first year, and this interval can be extended to six to 12 monthly and up to two to three yearly in long-term stable patients.[9, 12]

High risk MGUS: These patients should be referred to a haematologist and require more active initial evaluation and closer long-term monitoring. Risk factors include one or more of the following:

- Band size IgG > 15 g/L OR IgA or IgM > 10 g/L
- Any IgD or IgE monoclonal gammopathy regardless of concentration
- Symptoms or signs of a suspected multiple myeloma or lymphoproliferative disorder, e.g. bone pain or pathological fractures, constitutional symptoms such as weight loss, peripheral neuropathy, nephrotic syndrome
- Other unexplained laboratory or radiology abnormalities regardless of band size, e.g. hypercalcaemia, renal impairment, anaemia, lytic lesions or significant osteopaenia
- The presence of Bence-Jones proteinuria, immune suppression, age and sex are not in themselves prognostic. However, significant Bence-Jones proteinuria (>500 mg/L) should prompt haematologist referral because of the risk of development or progression of renal impairment.

Further evaluation usually includes bone marrow aspirate and trephine biopsy. Serum free light chains and beta-2 microglobulin may also be helpful in stratifying these patients – a normal light chain ratio and low beta-2 microglobulin level carries lower risk.

Understanding immunoglobulins

Plasma cells produce immunoglobulins which are composed of heavy and light chains. Each plasma cell produces only one type of heavy chain (IgA, IgD, IgG, IgM and IgE) and one type of light chain (either kappa or lambda [κ or λ]). After the chains are produced they are assembled within the plasma cell to form a whole immunoglobulin.

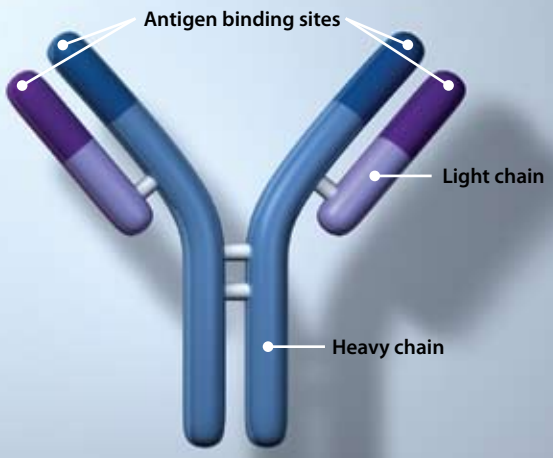

Figure 2: Immunoglobulin (showing light and heavy chains).

Other possible investigations for higher risk patients include; spine/pelvic MRI scan for possible lytic lesions, abdominal CT for retroperitoneal lymph nodes (in patients with IgM bands), and renal investigations including; possible renal/tissue biopsy for patients with unexplained nephrotic proteinuria or renal impairment (looking for amyloidosis).

Long-term patients with a high risk MGUS should usually be monitored at least several times in the first year, then annually for life. New symptoms or laboratory abnormalities should prompt earlier review. An increase in band size of more than 25% over three months (minimal 5 g/L) is regarded as significant.

Patients with asymptomatic multiple myeloma have significant risk (about 10% annually) of progression to symptomatic disease, and should be under haematologist review. A skeletal survey and a bone marrow aspirate and biopsy should be carried out at baseline. Laboratory tests and clinical work-up should be done at diagnosis including baseline MRI of the spine and pelvis. Tests should be repeated two to three months after the initial recognition of the diagnosis. If the results are stable, the studies should be repeated every four to six months for one year and, if stable, evaluation intervals can be lengthened to every six to 12 months. A skeletal survey should be performed if there is evidence of progression.

Routine follow-up tests for patients under long-term monitoring

These tests should include:[9]

- Serum protein electrophoresis with band quantitation
- Serum immunoglobulin levels
- Complete blood count
- Serum creatinine and eGFR
- Serum electrolytes
- Corrected serum calcium
- Urine for free light chains (Bence-Jones protein)

British/Nordic guidelines indicate there is no evidence to support measurement of serum free light chains in long-term follow-up monitoring and this is not formally recommended in either guideline (British/Nordic and IMWG).[9, 12]

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Routine laboratory testing during pregnancy

Most general practitioners no longer offer lead maternity care, however, may still be involved with the initial confirmation of pregnancy and first laboratory tests and general care during pregnancy. The following article provides guidance on appropriate testing in early pregnancy, throughout pregnancy and information about common changes to testing reference ranges during pregnancy.

Blood tests included in the first antenatal screen

When a woman becomes pregnant, it is recommended that she receives a range of standard investigations. A first antenatal screen is required even if the woman is considering termination of pregnancy.

The "first antenatal screen" may be requested by the GP at the first appointment when pregnancy is confirmed, and the results later forwarded to the chosen Lead Maternity Carer (LMC). If the woman is likely to enrol with a LMC in the near future, the tests can be delayed, at the patient's request, until her first appointment with the LMC.

Tests included in the first antenatal screen include:

- Complete blood count
- Blood group and antibody screen
- Rubella antibody status
- Syphilis serology
- Hepatitis B serology
- HIV

Prior to all laboratory testing in pregnancy, information should be provided to the pregnant woman about why the test is recommended, the implications of both a positive or negative result, the risk of disease transmission to the foetus (if relevant) and how the results will be delivered. Verbal consent (or decline) should be documented in the patients notes.[1]

Although the first antenatal screen usually occurs early in pregnancy, it may be requested at any stage of pregnancy, i.e. if a women presents for the first time late in pregnancy, she should still receive a first antenatal screen.

Complete blood count

A complete blood count (CBC) gives information on a number of haematological parameters, but generally in pregnancy the most useful are the haemoglobin, platelets and white blood cell count. Most laboratories will provide pregnancy adjusted reference ranges to enable easier interpretation.

Very low or high haemoglobin levels are associated with increased foetal risk.[2] Gestational age should be taken into account when assessing haemoglobin, as levels decrease during pregnancy due to haemodilution caused by increased plasma volume.[2] The lower limit for haemoglobin is usually 115 g/L, but for pregnant women the lower limit is usually reported as 100 g/L.

Iron deficiency anaemia is the most frequent haematological concern during pregnancy and is usually characterised by decreased haemoglobin, mean cell volume (MCV) and mean cell haemoglobin (MCH) levels. When iron deficiency is suspected, a measurement of serum ferritin should be used to confirm the diagnosis.[2]

Changes in platelet levels are frequently seen during pregnancy. A decrease in the platelet count is more common than an increase and is most obvious in women who had low levels prior to becoming pregnant. Platelets usually decrease as a result of haemodilution, and this can become more pronounced as the pregnancy progresses from the second to third trimester.[3] A platelet level of 150 x 10^9/L or less is abnormally low and should be discussed with a haematologist.

Elevated platelets levels during pregnancy are generally a reactive response to the pregnancy and do not usually suggest a clinical problem. However, due to the slightly increased risk of clotting, it would be advisable, when platelet levels are higher than 600 x 10^9/L, to discuss results with a haematologist.

The total white cell count will frequently be elevated in pregnancy due to increased numbers of neutrophils. Neutrophils can also demonstrate a "left shift" (increased number of band neutrophils). However, this neutrophilia is not usually associated with infection or inflammation.

The total white cell count can also be misleading in pregnant women and should be interpreted with care, e.g. elevated neutrophils with a low lymphocyte count may produce a total white count that falls within the reference range. Therefore the absolute count of each cell type is more useful than the total white cell count.

Blood group and antibody screen

Identifying ABO blood group, rhesus D status and red cell antibodies in pregnant women is important to prevent "haemolytic disease of the newborn" in subsequent pregnancies.

If the foetus is rhesus D-positive (and the mother is negative), the mother may form anti-D antibodies, which may affect a subsequent rhesus D-positive foetus. Anti-D antibodies can be formed during a range of situations, including amniocentesis, chorionic villus sampling (CVS), external cephalic version (ECV), bleeding during the pregnancy, major abdominal trauma and late miscarriage.

Haemolytic disease of the newborn in subsequent pregnancies, can be avoided by antenatal prophylaxis of commercial anti-D in the second and third trimesters, and post-natally.[2]

Rubella antibody status

All pregnant women should be screened for rubella antibodies. Contracting rubella during pregnancy presents a high risk of harm to the foetus. Congenital Rubella Syndrome occurs when the rubella virus infects the developing foetus, especially during the first trimester when up to 85% of affected infants will be born with a birth defect, e.g. deafness, eye defects, heart defects, mental retardation. The risk of birth defects is decreased when infection occurs after 20 weeks gestation.[4]

The aim of screening is to identify women who have not been immunised or have diminished immunity and are susceptible to contracting rubella, so they can be immunised in the postnatal period to protect future

Maternity care funding for general practice

Within the funding of primary maternity services in New Zealand, a clinician who is not the lead maternity carer may access funding for one pregnancy-related visit during the first trimester. In general practice, this funding may be used, for example, when a patient presents for confirmation of pregnancy and the first antenatal screen.

N.B. Consultations regarding a potential pregnancy are not eligible for this funding if pregnancy is not confirmed.

pregnancies.[2, 5] Rubella vaccination cannot be given during pregnancy (as it is a live vaccine) and if a mother contracts rubella during pregnancy there is no way to prevent transmission to the infant.[2]

Rubella antibody titres should be measured at each pregnancy as levels may decline and fall below protection levels. This is more often seen in people only exposed to the virus through immunisation.[6]

Interpreting low rubella titres in previously immune women

A rubella antibody level greater than 10 IU/mL usually indicates protection from the disease, however, re-infection with rubella has still been reported in women with antibody levels above 15 IU/mL. Therefore, pregnant women with rubella antibody levels less than 15 IU/mL should be advised to avoid coming into contact with people with rubella. Women with antibody levels less than 25 IU/mL, who have received only one dose of MMR, can be advised to have a second dose after delivery.[7]

Syphilis serology

All pregnant women should be screened for syphilis.[2] Mothers infected with syphilis can experience long-term morbidity and the complications for pregnancy are significant; 70 to 100% of infants will be infected and one-third will be stillborn.[2] In recent years rates of syphilis in New Zealand have been increasing (2006–2009).[8] However, latest surveillance data show that although syphilis infection is still a concern, rates now appear to be decreasing.[9]

Mother-to-child transmission of syphilis in pregnancy is associated with non-immune hydrops (a life-threatening condition of severe oedema in the foetus and newborn infant), intrauterine growth retardation, malformations and perinatal death. Infected infants, who do survive, often have long-term disabilities.[2]

Universal screening for syphilis in newly pregnant women is recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Women who test positive can then receive prophylactic antibiotic treatment. Penicillin is a safe and effective treatment for syphilis in pregnancy and can prevent congenital syphilis.[10]

The RANZCOG recommends that a treponemal test, e.g. Treponema pallidum particle assay (TPPA), is used to screen for syphilis as this can detect primary or secondary infection.[6]

Hepatitis B serology

Up to 85% of infants born to mothers infected with hepatitis B (particularly mothers who are HBeAg positive, i.e. with active infection), will become carriers and will be more likely to develop chronic liver disease, including cirrhosis, liver failure or liver cancer.[2, 11] Transmission of the hepatitis B virus from mother to infant can be prevented by administration of the hepatitis B vaccine and immunoglobulin to the infant at birth, therefore screening is important.[11, 12]

Women who are at increased risk of acquiring hepatitis B, e.g. women with sexual partners who are hepatitis B positive or intravenous drug users, are recommended to be vaccinated during pregnancy.[5]

HIV screening

All pregnant women should be screened for HIV. Women who are HIV positive can be given treatment to reduce the risk of HIV being transmitted to their infant (risk reduced from 32% to less than 1%).[1] Interventions to reduce mother-to-child transmission of HIV infection include antiretroviral therapy, elective caesarean section delivery and the avoidance of breastfeeding.[1, 2]

Any person undergoing a HIV test should be properly counselled about the implications of the test and the results, including how they wish to receive the results.

If a patient is considered at risk for HIV, hepatitis C screening should also be considered.

Best Practice Tip: In some DHB regions, HIV testing is automatically included as part of the antenatal screen, while in others, mothers must "opt on" for screening. The standard tick box for first antenatal screen does not always include HIV screening. Practices may wish to alter their electronic lab form to include an HIV tick box as a reminder to counsel patients on HIV screening and to add the test to the standard screen.

Additional testing in early pregnancy

Consider checking varicella antibody status in pregnant women with no (or uncertain) history of illness (i.e. chicken pox or shingles) or vaccination.[6] Contracting varicella during pregnancy is associated with a significant risk of harm to both mother and infant. There is a 0.7–2% risk of congenital varicella syndrome if varicella is contracted by the mother between eight and 20 weeks gestation.[13] Congenital varicella syndrome can cause blindness, growth retardation, limb and cranial malformations, delayed development, mental retardation, spontaneous abortion or foetal death. Contracting varicella between 25 to 36 weeks gestation increases the risk of the infant developing herpes zoster infection (shingles) after birth.[13] There is a 17–30% risk of serious disease in a newborn infant if the mother contracts varicella between five days before birth and two days after.[13]

As with the rubella vaccine, varicella is a live vaccine so cannot be given during pregnancy. Mothers with no (or diminished) immunity to varicella should consider immunisation to protect subsequent pregnancies.

If a mother with no history of varicella (and/or an absence of antibodies) is exposed to varicella during pregnancy, she may be offered either immunoglobulin (Zoster Immunoglobulin-VF) within 96 hours of exposure or acyclovir at the onset of symptoms. Treatment should be discussed with an infectious diseases physician. Zoster Immunoglobulin-VF is also recommended for:[14]

- Newborn infants who's mother has had chicken pox seven days before to seven days after delivery (not shingles)
- Hospitalised pre-term infants who's mothers have no history of chicken pox

A cervical smear may be considered at the first antenatal visit if the woman would be due for a routine test during the pregnancy (because as the pregnancy progresses, it may cause more discomfort to perform the test).[6] This is recommended by the RANZCOG who also states that there is no evidence that performing a smear is harmful to the foetus during pregnancy.[6] However, other countries such as the United Kingdom recommend that in most cases pregnant women should not have a cervical screening test, as pregnancy can make the results of the test more difficult to interpret and potentially inaccurate.[15] The decision whether to perform a routine cervical screening test during pregnancy should be based on clinical judgement and patient preference, taking into consideration factors such as previous abnormal smear results and time since last test.

Testing for chlamydia and gonorrhoea should be considered for those who may be at increased risk based on age (e.g. less than 25 years) and sexual history.[6]

Vitamin D is required for normal bone growth development in the foetus. Mothers with known vitamin D deficiency, or who are at risk for deficiency (e.g. dark skinned women, women who wear a veil) should receive vitamin D supplementation (cholecalciferol) without the need for testing.

For further information see "Vitamin D supplementation: navigating the debate", BPJ 36 (Jun, 2011).

N.B. Screening for toxoplasmosis or CMV infection during pregnancy is not routinely recommended in New Zealand.

Blood tests included in the second antenatal screen

At 26–28 weeks gestation, a second round of blood tests, commonly referred to as the "second antenatal" tests, is advised for pregnant women. In most cases the LMC will arrange these tests.

The second antenatal screen includes:

- 50 g glucose tolerance test (the "polycose" test)
- CBC
- Blood group antibodies

Screening for gestational diabetes

Gestational diabetes affects 5–8% of pregnant women and is associated with hypertensive disorders, macrosomia, shoulder dystocia, increased rates of caesarean delivery and the development of maternal diabetes later in life.[5, 16]

In New Zealand, it is recommended that testing for gestational diabetes occurs for all women between 26

and 28 weeks of gestation. Women at particularly high risk of gestational diabetes may be tested earlier.[17] Factors which increase the risk of gestational diabetes include; gestational diabetes in a previous pregnancy, family history of diabetes, belonging to a high risk ethnic group for diabetes, e.g. Māori, Pacific or South Asian (Indian).[17]

A 50 g glucose tolerance test (the polycose test) is used to screen for gestational diabetes. A 50 g glucose load is given to the non-fasting patient, and a glucose level is determined after one hour. Women with an elevated result should be followed up with a 75 g oral glucose tolerance test (OGTT).

Women who have had gestational diabetes during pregnancy should undergo an OGTT six to eight weeks after delivery. Even if not found to have diabetes at this time, women who have had gestational diabetes have an increased risk of developing type 2 diabetes within 15 years,[18] and should be screened with a fasting glucose test every one to two years.[17]

Repeat CBC and antibody screening

The CBC should be repeated at 28 weeks gestation, in particular to check haemoglobin and platelet levels (see commentary in previous section on how to interpret and manage these levels in pregnancy).

Antibody screening should also be repeated at 28 weeks gestation, to ensure no additional antibodies have developed. While blood group testing does not need to be repeated for subsequent pregnancies, the antibody screen should still be repeated.[2, 6]

Additional tests during pregnancy

Sub-clinical urine infection

It is recommended that all women have a mid-stream urine culture at the time of the first antenatal screen, again at the second antenatal screen and then at 36 weeks gestation, to exclude a sub-clinical urine infection (asymptomatic bacteriuria). Asymptomatic bacteriuria occurs in 2% to 10% of pregnancies and can lead to maternal pyelonephritis and may contribute to low birth-weight infants and pre-term birth (≤ 37 weeks).[19]

Screening for Group B Streptococcus

Group B streptococcal (GBS) infection is a significant cause of serious neonatal infection. Approximately 15–25% of women will be carriers, and one in 200 of these women will have infants who develop neonatal sepsis.[20]

Women may have a vaginorectal culture collected at 35 to 37 weeks gestation. Swabs may be collected by the patient, who has been instructed to swab the lower vagina first, and then rub the swab over the floor of the perineum to the anus, i.e. in a front-to-back direction. If positive for GBS, the mother should receive intrapartum antibiotic prophylaxis.[20]

Risk factors for GBS that would identify the need for intrapartum antibiotic prophylaxis include:[20]

- Pre-term labour, gestation ≤ 37 weeks
- Prolonged rupture of membranes ≥ 18 hours
- Maternal fever ≥ 38°C
- Previous GBS infected infant (prophylaxis required in all subsequent pregnancies)
- GBS bacteriuria during pregnancy (prophylaxis required in all subsequent pregnancies)

Testing for Down syndrome and other genetic conditions

Screening for Down syndrome, other chromosomal abnormalities and neural tube defects is offered to all pregnant women in New Zealand and testing can occur in either the first or second trimester of pregnancy.

Women need to be provided with enough information to make an informed decision about screening. Information should include the following:

- Reassurance that screening is voluntary
- Details of which screening options are available, the tests involved, the timing of the tests and where to go to get the tests
- Limitations of the tests, e.g. not all infants with the condition(s) being tested for will be identified, false positives are possible, testing is for specific conditions only and other abnormalities may be present
- Pamphlets explaining the different screening options are available from the National Screening Unit: **www.nsu.govt.nz**

First trimester screening is based on the combination of results of the following tests:

- Pregnancy-associated plasma protein A (PAPP-A)
- Beta-human chorionic gonadotropin (βhCG])
- Nuchal translucent (NT) scan

The PAPP-A and βhCG tests must be taken between nine and 13 weeks gestation (ideally between 10 and 12 weeks), and the NT scan carried out after 11 and before 14 weeks gestation.

Second trimester screening can be offered to all women who present after 14 weeks gestation but before 20 weeks, who have not completed first trimester screening (bloods are ideally taken between 14 to 18 weeks gestation). This serum screen measures βhCG, alpha-fetoprotein (AFP), unconjugated oestriol (μE3), and inhibin A.

If the results of either first or second trimester screening indicate an increased risk of foetal abnormalities, the mother should be referred to an obstetrician.

N.B. Women can only access one publically funded screening option. If they have the first trimester screening option, the blood tests will be fully funded and there is no cost to the patient, however, the NT scan may have a part-charge. The second trimester blood tests will be fully

Summary of routine antenatal tests

Laboratory	
Initial tests "First antenatal"	☑ CBC ☑ Blood group and antibodies ☑ Rubella ☑ Syphilis ☑ Hepatitis B serology ☑ HIV ☑ Urine culture
26–28 weeks "Second antenatal"	☑ CBC ☑ Polycose ☑ Antibodies ☑ Urine culture
35–37 weeks Group B streptococcal (GBS) infection (if risk factors)	☑ Vaginal swab ☑ Urine culture
Testing for genetic conditions (only one option applies)	
First trimester screening 11– <14 weeks	☑ NT scan ☑ Blood tests for PAPP-A, βhCG (3–4 days before scan)
Second trimester screening 14–18 weeks	☑ βhCG ☑ AFP ☑ μE3 ☑ Inhibin A

funded providing the women has not already accessed the first trimester screening. All sections of the laboratory referral form need to be filled out (including maternal age and weight, gestation and family history) to allow for an accurate risk prediction.

Woman at increased risk of foetal chromosomal abnormality, i.e. aged 35 years and over or have a family history of chromosomal disorder, should be referred to an obstetrician early in their pregnancy, to discuss the option of chorionic villus sampling (CVS) or amniocentesis.

CVS is usually performed at 11–12 weeks gestation and amniocentesis at 14–18 weeks gestation. These tests allow a more accurate prenatal diagnosis of chromosomal abnormality, but are associated with an increased risk of harm to the foetus including; infection, amniotic fluid leakage and miscarriage.

An ultrasound scan is offered to all pregnant women at 18–19+ weeks gestation to check foetal anatomy for any abnormalities.

Changes to reference ranges during pregnancy (adapted from Kyle, 2008)[21]

Analyte	Effect of pregnancy	Notes
Alpha-fetoprotein (AFP)	↑	Peaks in last trimester
Alkaline phosphatase (ALP)	↑	Marked increase due to placental izoenzyme
Blood volume	↑	Increases by 20–30%
Ca125 (tumour marker)	↑	2–2.5 times increase in first trimester
Cholesterol	↑	Up to 40% increase
Creatinine clearance	↑	
ESR	↑	Increasing to 30–60 mm/hr as pregnancy progresses
Iron binding	↑	Significant increase
White blood count	↑	May increase to 15–18 x10^9/L
CRP	↑	
Haemoglobin	↓	Decreases as a result of haemodilution due to greater blood volume
FT4	↓	May decrease up to 20% in late pregnancy
TSH	↓	Often decreases first trimester, but then returns to normal levels

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QUIZ FEEDBACK

Thrombophilia, CRP, fungal infections

Introduction

This quiz feedback provides an opportunity to revisit Best Tests, March 2011, which focused on; the role of thrombophilia testing in general practice, the collection of specimens when investigating fungal infections, and an update on the role of ESR and CRP when investigating temporal arteritis. All general practitioners who responded to this quiz will receive personalised online feedback and CME points.

1.	**Which of the following most increases an individual's risk of venous thromboembolism (VTE)?**		
		Your peers	Preferred
☐	Major trauma	96%	✓
☐	Varicose veins	8%	
☐	Air travel	12%	
☐	Inherited thrombophilia	22%	

Comment:
The strongest risk factors for VTE are; fracture (hip or leg), hip or knee replacement, major general surgery, major trauma and spinal cord injury. Inherited thrombophilia is considered to be a moderate risk factor, while air travel and varicose veins are weak risk factors. The assessment of risk can help to determine if the event was provoked (i.e. exacerbated by external risk factors), or unprovoked (i.e. occurred for no apparent reason).

2.	**In which of the following situations is thrombophilia testing indicated?**		
		Your peers	Preferred
☐	A person under the age of 40 years, presenting with unprovoked VTE, and no known family history of VTE	72%	
☐	A person on chemotherapy presenting with VTE	6%	
☐	A woman on oral contraceptives, worried about the risk of VTE	3%	
☐	All people presenting with VTE	4%	

N.B. None of the options are correct.

Comment:
Thrombophilia testing should only be performed when the test results will alter management and is therefore only recommended in situations such as:

- A patient presenting with unprovoked venous thrombosis at an early age (<40 years) **with a family history of thrombosis** (more than two other symptomatic first degree family members)
- Children with purpura fulminans
- Pregnant women at risk of venous thrombosis, e.g. pregnant women who have had a previous VTE due to a minor provoking factor

Thrombophilia testing is not indicated in any of the scenarios presented in Question 2. In hindsight this may have caused confusion. In the first option, testing would have been indicated if "a positive family history of thrombosis" was added to the scenario. Malignancy and oestrogen containing oral contraceptives are both

moderate risk factors for VTE but are not considered indications for testing. In addition, testing is not recommended when patients present in the acute phase of a thrombotic event.

3.	**What is the purpose of the D-dimer test, when investigating a possible deep vein thrombosis (DVT)?**	Your peers	Preferred
☐	An elevated test is a specific marker for DVT	1%	
☐	Is a useful test for helping to exclude DVT	86%	✓
☐	Is useful for differentiating between a superficial and deep vein thrombosis	2%	
☐	Should be used in conjunction with a clinical probability rule for determining referral to ultrasound	73%	✓

Comment:
The D-dimer test can be elevated in nearly all patients with VTE, but can also be elevated in patients with infection, malignancy or recent surgery so is therefore not specific. Its key diagnostic role is as a negative predictor of VTE, i.e. a low level makes VTE an unlikely diagnosis. D-dimer can be used in conjunction with the Wells Rule or the Primary Care Rule to determine the probability of a DVT.

Differentiating between superficial and deep thrombosis is best done with ultrasound.

4.	**If a patient wants to start the combined oral contraceptive (COC), which of the following are correct?**	Your peers	Preferred
☐	The patient should have thrombophilia testing performed	<1%	
☐	Ask about any known inherited thrombophilia	89%	✓
☐	Do not prescribe the COC if there is any first degree relative with a history of VTE	47%	+/–
☐	COC are a moderate risk factor for VTE	80%	✓

Comment:
The use of oestrogen-containing oral contraceptives is a moderate risk factor for VTE but this is not considered an indication for testing.

It is important to ask about a family history of thrombophilia, to determine if a first degree relative aged less than 45 years has had a VTE. If this is the case, the use of oestrogen-containing oral contraceptives is not recommended unless other methods are unacceptable or not available. For patients with known thrombogenic mutations, oestrogen-containing oral contraceptives should be avoided.

5.	**Your patient reports a positive family history of VTE (her elderly mother had a DVT following a hip fracture). What is the role of thrombophilia testing in your patient?**	Your peers	Preferred
☐	Testing is indicated	6%	
☐	Family members should be tested	1%	
☐	She should be advised to avoid long-distance flights	5%	
☐	It would be useful to test for just the more common mutations (Factor V Leiden and Prothrombin gene mutations)	32%	

Comment:
As previously discussed, one of the strongest risk factors for VTE is fracture (hip or leg) so in this scenario no testing is indicated for either your patient or for her mother.

Factor V Leiden and Prothrombin gene mutation are considered low risk thrombophilias, and case finding in asymptomatic relatives is not indicated.

6.	What next steps are recommended in a person suspected of temporal arteritis with an elevated CRP, but normal ESR?	Your peers	Preferred
☐	Repeat ESR	2%	
☐	Repeat CRP	3%	
☐	The ESR and CRP should both be elevated to support diagnosis	<1%	
☐	Biopsy or empirical treatment should be initiated, irrespective of results	98%	✓

Comment:
In most cases, temporal arteritis is characterised by a normal ESR with an elevated CRP, however, although unusual, an elevated ESR and a normal CRP can also be suggestive of temporal arteritis. Traditionally, both ESR and CRP have been used to investigate temporal arteritis, but the role of ESR as a routine test for this has now been questioned. Some consider the additional 1.7% sensitivity that is gained by using both ESR and CRP together, encourages increased use of tests, but for minimal clinical gain. Particularly, as any patient with a strong clinical history should have a temporal artery biopsy or empirical treatment irrespective of the results of laboratory tests.

7.	In which of the following scenarios is fungal testing indicated?	Your peers	Preferred
☐	In suspected fungal infection of the hair where the diagnosis is uncertain	80%	✓
☐	In all patients with suspected athletes foot	2%	
☐	To allow targeted treatment	86%	✓
☐	In all patients with thick, crumbly toenails	15%	

Comment:
Most minor fungal infections, e.g. athletes foot, do not require testing and can be treated topically. Laboratory fungal testing is useful to confirm disease when it is chronic, severe or when considering systemic therapy, and when the fungal infection involves the hair, palms of the hands or soles of the feet. Sometimes testing can be useful to determine the species of fungus to allow targeted oral treatment.

Thick, crumbly toenails can be the result of various conditions, not just fungal infection. Laboratory testing might not be useful in cases where patients are not willing to take oral antifungal therapy, even if a fungal infection was confirmed.

8.	Which of the following may be reasons for a negative fungal result?	Your peers	Preferred
☐	Use of antifungal medication prior to collection	98%	✓
☐	Lack of viable fungal elements in a sample	95%	✓
☐	The lesion is a discoid eczema	88%	✓
☐	Cleaning the area with alcohol prior to collection	9%	

Comment:
When collecting specimens for fungal testing, preparation of the skin or nails with an alcohol swab is useful to remove any traces of skin products or medications.

Negative culture results may arise due to a number of problems including; antifungal treatment used prior to collection of the specimen, the presence of non-viable hyphae elements (as can occur in the distal region of a nail) and an incorrect clinical diagnosis, such as the skin condition actually being a skin cancer or form of eczema.

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