

QML PATHOLOGY

newsletter november 06

>> Low Molecular Weight Heparin (LMWH) - Clinical Guidelines Dr Peter Davidson, Pathologist in Charge - Haematology

To aid the treating Doctor, we have devoted the November 2006 newsletter to clinical guidelines in the use of LMWH.

As of 1 December 2006, QML Pathology's Warfarin Care Clinic will be unable to accept patients who have a Local Medical Officer and are not under the direct care of a private specialist while on heparin. When the patient's heparin is completed and their INR is at an acceptable level, the QML Pathology Warfarin Care Clinic will be able to take over the patient's warfarin monitoring. We appreciate that this will require a slightly longer period of clinical involvement by the Medical Officer, however it is hoped this will provide a more clinically satisfying outcome for the patient and Doctor.

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>> Low Molecular Weight Heparin (LMWH) - Clinical Guidelines

Dr Peter Davidson, Pathologist in Charge - Haematology

OVERVIEW

Low molecular weight heparin (LMWH) is used in both the prevention and treatment of thrombo-embolic conditions. It has replaced unfractionated heparin therapy (UFH) in many settings as the drug of choice for a variety of reasons.

Limitations of Unfractionated Heparin

Most of the limitations of unfractionated heparin are explained by its non-specific binding to cell surfaces and plasma proteins.

- *Unpredictable anticoagulant response:* The bioavailability of unfractionated heparin is reduced when it is given by subcutaneous compared with intravenous injection. Therefore, therapeutic doses of unfractionated heparin must be closely monitored, with dose adjustment according to the results of the activated partial thromboplastin time (APTT).
- *Heparin resistance:* Non-specific binding of unfractionated heparin to plasma proteins is the most common cause of heparin resistance, defined as requiring a dose in excess of 35 000 IU over 24 hours to prolong the APTT into the therapeutic range.
- *Heparin-induced thrombocytopenia:* Immune heparin-induced thrombocytopenia (HIT) occurs in 1–3% of patients treated with unfractionated heparin, usually between 5 and 15 days after heparin treatment is started. In some patients who develop immune heparin-induced thrombocytopenia, the platelet count may not fall until after the onset of thrombosis. Whereas, LMWH has a < 1% incidence of inducing HIT.
- *Osteopenia:* Unfractionated heparin causes osteopenia by binding to osteoblasts, which stimulates osteoclast activation and results in bone breakdown. This is particularly relevant in patients requiring long-term anticoagulation therapy, who cannot be treated with oral anticoagulants such as during pregnancy.

Advantages of Unfractionated Heparin

Unfractionated heparin retains a role in the treatment of patients at high risk of bleeding or in whom rapid reversal of anticoagulation may be required. Unlike LMWH, unfractionated heparin has a short half-life after intravenous injection (1–2 hours), can be reversed by protamine sulfate and its plasma clearance is not dependant on renal excretion. Therefore, unfractionated heparin remains the parenteral anticoagulant of choice in intensive care units, operating theatres and for patients with marked renal impairment.

INDICATIONS

In neonates and children the low molecular weight heparin of choice is 'Enoxaparin' (Clexane). Currently this is the only form of LMWH available in Australia with which dose-finding studies in children have been performed. In obstetric patients, the LMWH of choice may be 'Dalteparin' (Fragmin). In other adults

the choice depends on the clinical scenario, but Clexane has been approved in many scenarios.

LMWHs are used for the prophylaxis or treatment of deep vein thrombosis (DVT). The decision to use LMWH instead of standard heparin or warfarin will depend upon the clinical scenario and individual patient factors, such as risk of bleeding or availability of venous access. The anticoagulant effect of LMWH can extend beyond 24 hours after administration.

Clinical Indications

Medically Necessary:

The use of LMWH in the outpatient setting is considered medically necessary for any of the following conditions:

1. DVT/PE

a. Treatment

- *Acute:* May be initiated on an outpatient basis in eligible patients in conjunction with warfarin, continued for at least 5 days, and discontinued when the international normalized ratio (INR) is in the therapeutic range (2 - 3)
- *Long Term:* Treatment for 3 to 6 months following acute DVT in patients who have cancer or in whom warfarin is contraindicated or not tolerated

b. Prevention

For prevention of DVT post-operatively in the case of the following procedures:

- Hip fracture or total hip replacement surgery given for up to 5 weeks post-procedure
- Knee replacement surgery given for up to 10 days post-procedure
- Major general or vascular surgery for patients at high risk for venous thromboembolism (VTE) due to malignancy, history of DVT or pulmonary embolism (PE) or other comorbidity - given for up to 4 weeks post-discharge
- Gynaecological surgery for patients at high risk for VTE including surgery for malignancy, age > 60 years or previous VTE – given for up to 4 weeks post-discharge

2. Pregnancy

- Treatment or prevention of thrombophilic disease or VTE in pregnancy (For women on long-term warfarin treatment, LMWH should be substituted when pregnancy is achieved. Note that for women with mechanical valves – UFH may be the heparin of choice)

3. Thrombophlebitis

- Treatment of spontaneous superficial thrombophlebitis given for up to 4 weeks

4. Acute Coronary Syndromes

- Treatment of Non-ST-segment-elevation acute coronary syndromes / Unstable Angina for up to 7 days



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5. Miscellaneous

- Patients for whom long-term warfarin treatment is generally indicated and appropriate (for example, following a DVT in a patient who does not have cancer) **but** who are intolerant or have contraindications to warfarin, or develop recurrent VTE while on therapeutic doses of warfarin (i.e. INR in the appropriate therapeutic range)

Warnings and Precautions

- *Heparin-induced Thrombocytopenia*
Clexane should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis.
- *Concomitant use of therapeutic doses of other anticoagulants/ anti-platelet agents*
It is recommended that agents which affect haemostasis should be discontinued prior to, or dove-tailed cautiously with Clexane therapy unless strictly indicated. These agents include medications such as:
 - Systemic salicylates, acetylsalicylic acid and NSAIDs including ketorolac
 - Dextran 40, ticlopidine and clopidogrel
 - Thrombolytics and anticoagulants
 - Other anti-platelet agents including glycoprotein IIb/IIIa anticoagulants

If the combination is indicated, Clexane should be used with careful clinical and laboratory monitoring when appropriate.

- *Renal Impairment*
Since exposure of Clexane is significantly increased in patients with severe renal impairment (creatinine clearance <30 ml/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical observation is advised.

DOSING

Infants and Children - Enoxaparin

	Patients < 2 mths	Patients 2mths-18yrs
Treatment Dose	1.5mg/kg/dose BD	1mg/kg/dose BD
Prophylactic Dose	0.75mg/kg/dose BD	0.5mg/kg/dose BD

Adults - Enoxaparin / Dalteparin

	Enoxaparin	Dalteparin
Treatment Dose	1.5mg/kg daily or 1mg/kg/dose BD	100 Units/kg/dose BD
Prophylactic Dose	20 – 40mg daily	2500-5000 Units daily

Renal Failure Adults (eGFR <30) – Enoxaparin
No dose adjust is required if eGFR is > 30

	Clexane	UFH
Treatment Dose	1mg/kg/dose daily	IV UFH may be preferred
Prophylactic Dose	0.5mg/kg daily up to 30mg daily	

Adults - With extremes of Wt (eg. BMI < 20 or > 40)

	High BMI	Low BMI
Treatment Dose	Base on total body weight unless patient has very extreme BMI	Dose as usual
Prophylactic Dose	30-60mg daily	0.5mg/Kg daily

Adverse Effects

- *Haemorrhage*
As with other anticoagulants, bleeding may occur in the presence of associated risk factors such as organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis. LMWHs can cause minor bleeding (e.g. easy bruising, gum bleeding after brushing teeth) as an undesirable adverse effect – a soft toothbrush, waxed dental floss and an electric shaver are recommended to minimise bleeding.
- *Thrombocytopenia*
Mild, transient, asymptomatic thrombocytopenia has been reported during the first days of therapy. Rare cases of immuno-allergic thrombocytopenia with thrombosis (i.e. true HIT) have been reported.
- *Local Reactions*
Pain, haematoma and mild local irritation may follow the subcutaneous injection of Clexane. Rarely, hard inflammatory nodules, which are not cystic enclosures of Clexane, have been observed at the injection site. They resolve after a few days and should not cause treatment discontinuation. Exceptional cases of skin necrosis at the injection site have been reported with heparins and LMWH's. These phenomena are usually preceded by purpura erythematous plaques, infiltrated and painful. Treatment with Clexane must be discontinued.

MONITORING

- All patients require some form of monitoring:
- Baseline: CBC, PT/INR, APTT (optional)
 - First 2 weeks of LMWH: CBC days 3,5 then every 2 – 3 days
- If there is an abrupt decrease in the platelet count (approx. 50%) consideration must be given to the possibility of Heparin Induced Thrombocytopenia (HIT)
 - Ongoing therapy: CBC weekly for weeks 3 and 4 then every 4 weeks
 - Clinical observation
 - Coagulation assays to assess for accumulation where indicated

In most clinical situations, coagulation monitoring of LMWH is not required.



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Indications for coagulation monitoring of LMWH include:

- Moderate or severe renal insufficiency (calculated creatinine clearance < 30 mL/min)
- Low body weight (< 40 kg)
- Obesity (> 140 kg or BMI > 40kg/m2)
- Pregnancy
- AT deficiency
- Recurrent thrombosis or excessive bleeding despite apparent adequate dosing

The recommended test for monitoring LMWH is an antifactor Xa assay (heparin assay). An antifactor Xa assay standard curve must be constructed for each LMWH preparation used in the care system. Appropriate commercial controls can be used if available.

APTT reagents show variable sensitivity to LMWH. Although the APTT may be prolonged in patients on LMWH, it does not reliably reflect LMWH activity, as the degree of prolongation is not marked in contrast to UFH because of the low anti-thrombin: anti-X ratio of LMWH. Thus, APTT is NOT the recommended test for monitoring LMWH. However, one can reasonably suspect that if the APTT is > 10sec above the normal range that the anti-Xa is probably above the desired therapeutic range.

When to Test

- 3 – 5 hours post-dose (peak level)
- Patient should have received LMWH for 48-72 hours prior to initial test - 48 hrs for daily regimes; 72 hrs for BD regimes
- Pregnancy - If using a therapeutic protocol, progress anti-Xa testing will be required monthly. If using a prophylactic regime, no testing unless there is a co-existing indication

Suggested therapeutic range for:

- Twice-daily dosing is 0.6 to 1.0 IU/mL obtained 4 hours after subcutaneous injection
- Once-daily dosing is 1.0 to 2.0 IU/mL (1.3 -1.7 IU/ml is probably ideal) obtained 4 hours after subcutaneous injection
- If checked for Trough levels should be > 0.2 IU/ml but < 0.5 IU/ml

Suggested prophylactic range for:

- Twice-daily dosing is 0.4 to 0.6 IU/mL, obtained 4 hours after subcutaneous injection

Nomogram for Low Molecular Weight Heparin Therapy

The table below outlines dose adjustments required for a given anti-Factor Xa result in patients requiring therapeutic anticoagulation with LMWH.

Correction of Supratherapeutic Anticoagulation caused by LMWH

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supratherapeutic anticoagulation with LMWH.

Reversal of LMWH with protamine sulfate may be incomplete, with neutralisation of 60 to 75% at most. However, protamine should be considered in patients with severe life-threatening bleeding.

Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension. Protamine can exert its own anticoagulant effect if used in doses larger than required for reversal.

Dosage

If LMWH has been administered within the last 8 hours:

- First dose: 1 mg protamine per 100 anti-factor Xa units LMWH *
- If second dose required because of on-going bleeding: 0.5mg protamine per 100 antifactor Xa units LMWH*

If LMWH has been administered more than 8 hours ago:

- First dose: 0.5 mg protamine per 100 antifactor Xa units LMWH *

** 1 mg enoxaparin - approximately 100 antifactors Xa units administration*

- Inject the calculated dose of protamine sulfate into a 100 mL bag of 0.9% NaCl (saline)
- Protamine sulfate administered by slow IV infusion over 10 minutes partially reverses the anticoagulation effects of LMWH

Nomogram for Low Molecular Weight Heparin Therapy

anti-Xa level (units/mL)	? Hold Next Dose	? Dose Change	? Repeat anti-Xa level
< 0.35	No	Increase by 25%	4 hours post next a.m. dose
0.35-0.49	No	Increase by 10%	4 hours post next a.m. dose
0.5-1.0	No	No change	Once/week 4 hours post an a.m. dose
1.1-1.5	No	Decrease by 20%	4 hours post next a.m. dose
1.6-2.0	3 hours	Decrease by 30%	Trough level pre next dose, then 4 hours post next a.m.dose
> 2.0	Until anti-Xa level <0.5 units/ml	Decrease by 40%	Trough level pre next dose and if not <0.5 units/ml repeat BD

NB: The above nomogram assumes there is no bleeding.
Patients receiving LMWH should be monitored for heparin induced thrombocytopenia (HIT) with a platelet count beginning at baseline, then every other day.

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Check Anti-Factor Xa Levels

- Obtain blood 15 minutes after the completion of the infusion and check the anti-Xa level
- Rebound anticoagulation can occur so it would be prudent to monitor the anti-Xa level - probably at least twice in the next 24 hours at 4 hrs and 12 hrs respectively. More than one infusion of protamine sulfate may be required for adequate reversal
- Persistent bleeding – if significant bleeding persists despite the use of protamine and FFP, then r-F VIIa is indicated

Do not exceed 50mg per dose over a short period.

Other Precautions

Spinal or Epidural Anaesthesia or Spinal Puncture

Regional anaesthesia should be avoided in patients with a history of abnormal bleeding or if taking medications that affect haemostasis (e.g. aspirin, NSAIDs, platelet inhibitors, warfarin).

Bleeding or haematomas within the spinal column may result when a heparin product or fondaparinux is used concurrently with spinal or epidural anaesthesia or spinal puncture. The risk for complication increases with placement or removal of catheters in the spinal canal and by traumatic or repeated epidural or spinal puncture. Use of other drugs affecting the blood clotting mechanism, such as NSAIDs, platelet inhibitors or other anticoagulants, also increases the risk of complication.

- If a regional anaesthetic is administered, a single-dose spinal anaesthetic is preferable to continuous epidural anaesthesia
- Placement of a catheter should be delayed for 10-12 hours after administration of prophylactic doses of LMWH e.g. Clexane 20 mg or 40 mg once daily. Patients receiving higher doses of Clexane (1 mg/kg twice daily or 1.5 mg/kg once daily) will require longer delays (24 hours).
- If a continuous epidural anaesthesia is administered, the decision to implement LMWH prophylaxis in the presence of an indwelling catheter must be made with extreme care. If LMWH prophylaxis is administered while the patient is receiving continuous epidural anaesthesia, the patient must be monitored carefully for early signs of cord compression (e.g. progression of lower extremity numbness or weakness, bowel or bladder dysfunction).
- If LMWH prophylaxis is administered while the patient is receiving continuous epidural anaesthesia, removal of the catheter should be delayed at least 10 to 12 hours after the dose of LMWH. Regional anaesthesia should be avoided

if there is a haemorrhagic aspirate during insertion of the spinal needle.

- If blood is present during needle/catheter placement, the subsequent dose of Clexane should be delayed for 24 hours after placement.
- LMWH prophylaxis should be delayed 2-4 hours after placement of the spinal needle or removal of the catheter.
- Commencement of NSAIDs should also be delayed 4-6 hours after removal of the catheter.
- Carefully monitor patients for possible spinal or epidural bleeding. Treat immediately if neurological impairment is detected.

For further information please do not hesitate to contact one of our Haematologists on (07) 3121 4444.



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Dr Paul Monagle and Thirza Titcher (Pharm)

Royal Women's and Children's Health Melbourne

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BEATRICE K. H. IP*, AMANDA R. THOMSON* AND HELEN T. MORIARTY†

*Haematology, Concord Repatriation General Hospital, Concord,

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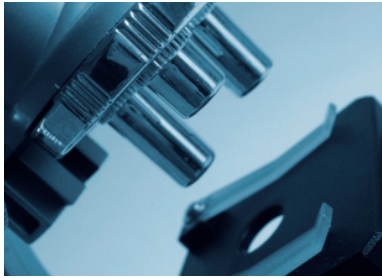
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WARFARIN DOSING OVER THE CHRISTMAS PERIOD

Over the upcoming Christmas period, the QML Pathology Warfarin Care Clinic will be closed. Please note that no new registrations will be taken from 8pm on Thursday 21 December 2006, with the registration line re-opening at 7am on Tuesday 2 January 2007. During this period it is essential that any new patients on warfarin are supplied with instructions, as QML Pathology will be unable to monitor

them until we re-open in January. Unfortunately QML Pathology cannot provide warfarin control for patients under a period of 4 weeks. As a result, we would appreciate if you could arrange a colleague to supervise any warfarin patients you control while you are on leave. Please note that this also applies to interstate patients on holiday in Queensland.



QML updates november 06



The Spirit of Giving

The festive season is an occasion when we reflect on the year that has been and show genuine gratitude for the people who have supported us throughout this time. Historically QML Pathology has expressed our thanks with a small token of appreciation for members of the medical community. However, for the past three years we have been fortunate to have the opportunity to convey our thanks through a donation to those in the community who are less privileged than ourselves.

Our Christmas donation is something each of you is a part of. It is because of your continued patronage that we have the opportunity to make a crucial difference in the lives of others. As a result of your support two charities will have the chance to convert \$50 000 into life-changing experiences. In 2006 these charities are Angel Flight and Zoe's Place (A Hospice for Children); two exemplary charities who, like you, support patients throughout their difficult medical and terminal illnesses.

Angel Flight

When five children were left 1500kms away from their mother at Christmas, Angel Flight took a very keen interest. With their mother awaiting a liver transplant in Brisbane, the five Townsville children were left to spend Christmas without one of the most important members of their family. However, thanks to Angel Flight and the generosity of their pilots five children boarded a plane on Christmas Eve to receive an invaluable gift – Christmas with their mother.

This flight is only one of over a thousand coordinated each year by Angel Flight. Recognising that illness is traumatic enough without the absence of loved ones, Angel Flight was established. Angel Flight coordinates non-emergency flights for people who have a financial and medical need of assistance. It ensures that people as far west as Birdsville and north as Cairns make their journey to the city for medical treatment without a road trip their body cannot tolerate. It also makes sure they do not have to make this journey alone, but that their family can be with them for support every step of the way. For further information or to make a donation please call (07) 3852 3300 or visit www.angelflight.org.au.

Zoe's Place

There is nothing more tragic than a parent outliving their child; however it is an unfortunate reality for a number of families. Working in a medical environment, many of you will have seen the incredible toll a life-threatening illness takes on a child and their family. Zoe's Place is an organisation dedicated to providing a comprehensive support network in these situations. A unique venture, Zoe's Place is the only purpose-built facility providing respite, hospice, palliative and end of life care services for children and families across the state.

While the growing need for a service of this kind is heart-breaking, its availability is of the utmost importance. So often, terminally ill children spend their final days in a hospital ward or intensive care unit. What Zoe's Place offers is a medically supported alternative that allows the whole family to be together in a private and supportive environment. With emergency respite and counselling services also available, Zoe's Place is committed to helping the family unit remain intact throughout this difficult journey in their life. For further information or to make a donation please call (07) 3376 6655 or visit www.zoesplace.com.au.

It is rewarding to have the opportunity to support those charities which give such wonderful support to patients during some of the most difficult moments in their lives. Thank you to every member of the medical community, your support has enabled QML Pathology to help these charities make a difference in the lives of others.

New Collection Centres

Mitchelton

Shop 114B, Brookside Shopping Centre
Osborne Road
Phone: (07) 3355 0359
Opening Hours: Monday to Friday 7.00am – 11.00am

Pacific Pines

Unit 8a, Pacific Health Medical Centre
Corner Pacific Pines Boulevard & Pitcairn Way
Phone: (07) 5573 4751
Opening Hours: Monday to Friday 8.00am - 1.00pm

Relocated Collection Centres

Edmonton

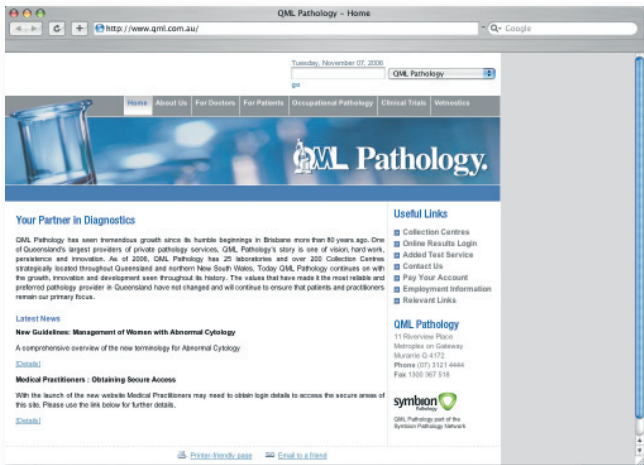
Shop 5A, Piccones Shopping Village
114 Bruce Highway
Phone: (07) 4055 5622
Opening Hours: Monday to Friday 8.00am – 4.30pm
(closed for lunch 12.30pm – 1.30pm)

Kippa-Ring

Shop 40, Kippa-Ring Village Shopping Centre
284 Anzac Avenue
Phone: (07) 3883 1558
Opening Hours: Monday to Friday 7.30am – 6.00pm



QML updates november 06



www.qml.com.au

Many of you may be aware that we have recently launched a more functional website at www.qml.com.au.

With a fresh new look, the relaunch of the QML Pathology website aims to provide a more comprehensive site with a host of useful features and easier navigation. While the site continues to provide the publications you regularly refer to, it incorporates a number of new and upgraded features that can assist in your daily practice:

- Online ordering of pathology products, such as urine jars, blood tubes, patient information brochures
- Online ordering of travel health information and vaccines
- Patient testing information
- Online ordering of added tests
- Online registration for online results

In the coming months the site will continue to evolve with the introduction of online registration for warfarin patients, along with numerous other features.

Note: With the launch of the new website Medical Practitioners may need to obtain login details to access secure areas on the site. Please use the latest news link located on the homepage to view further details. If you are currently registered to receive Online Results your login details will allow you access to all secure areas on the new website.

All in all, the new website brings our web presence in line with the quality and accuracy you have come to expect from QML Pathology. For further information please visit www.qml.com.au.

Doctor's Noticeboard

- Dr Frank Carmody, Obstetrician & Gynaecologist, would like to advise that he has medical suites available for sessional or permanent lease at Sunnybank. Consulting rooms are situated opposite Sunnybank Private Hospital and include an adjacent procedure room, wiring for internet access and a range of nearby support services with undercover parking available. Please direct any enquiries to Jenny on (07) 3371 4933
- Dr Peter Gourlas, General Surgeon, would like to advise that he has commenced in private practice at Greenslopes Private Hospital. He continues to consult at the Princess Alexandra and Ipswich General Hospitals in their Colorectal Departments. Dr Gourlas performs Colorectal, Laparoscopic and General Surgery, with the inclusion of Colonoscopies. His contact details are as follows:

Phone: (07) 3324 1114
Fax: (07) 3324 1115
Mobile: 0413 756 474
Email: drpetergourlas@hotmail.com

Upgrading to Medical Director 3?

If you are considering upgrading from version 2 of Medical Director to version 3, please remember to contact the QML Pathology EDI Support Desk. By dropping them a quick email, they can ensure your results continue to be available within the new Medical Director software. To make the transition as smooth as possible or for more information please do not hesitate to contact the QML Pathology EDI Support Team on 1300 738 448 or edihelp@qml.com.au.

Semen Analysis

It is extremely important to stress the significance of timeframes to patients who are delivering a sample for seminal analysis. Once the semen collection is made it should be kept at body temperature and delivered to the clinic as soon as possible, ensuring it occurs within an hour of them having made the collection. This is vital if we are to get an accurate result.

Advice on seminal collection is available in our Patient Testing Instruction sets or on www.qml.com.au. If you do not have copies of this instruction sheet, please do not hesitate to contact your local Medical Liaison Officer for assistance.