



Avian Influenza A strain H5N1

by Dr David Drummond

AT PRESENT, Viet Nam and Thailand are the only two countries in which human cases of avian influenza A (H5N1) virus infection are known to have occurred in the current outbreak. The first recorded outbreak of H5N1 infection in humans occurred in Hong Kong in 1997, when 18 persons developed serious disease and 6 died. The present human cases in Viet Nam and Thailand coincide with an historically unprecedented spread of highly pathogenic H5N1 avian influenza in the poultry populations of Asian countries. Since mid-December 2003, outbreaks of avian influenza A (H5N1) disease in poultry have been confirmed in the Republic of Korea, Viet Nam, Japan, Thailand, and Cambodia.

Additional countries [Indonesia, China and Pakistan] have detected deaths in poultry flocks, and the cause is currently under investigation.

The World Health Organisation (WHO) has identified the rapid culling of H5N1 infected or exposed poultry as the major line of defence for preventing further human cases and possibly averting the emergence of a new influenza virus capable of causing an influenza pandemic. At present the WHO has not recommended travel restrictions to affected areas.

At present, there is no evidence of person-to-person transmission. The human cases to date are believed to be from contact with chickens or their waste. The infection cannot be transmitted via eggs or properly cooked poultry.

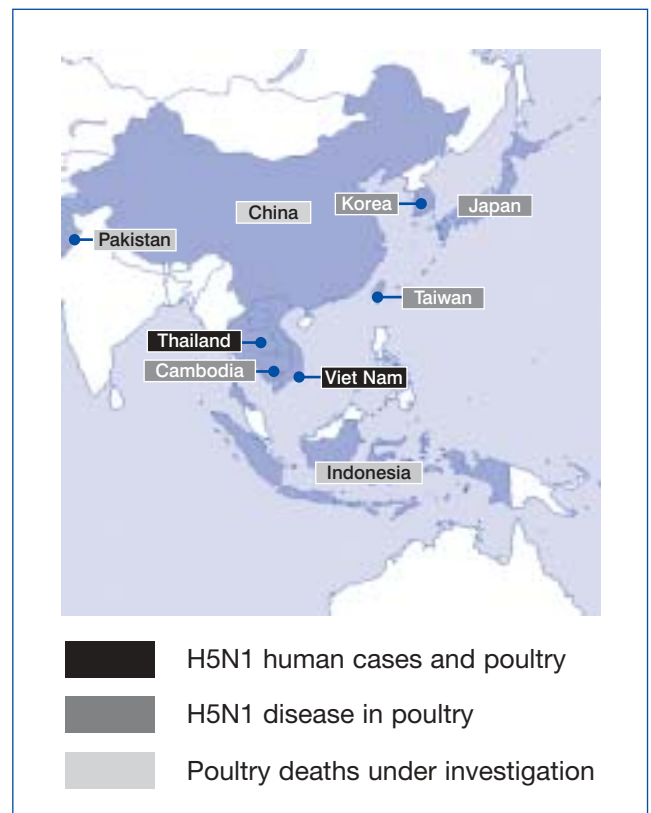
The principal concerns are as follows:

1: Epidemiology

The rapid and extensive spread of the H5N1 Influenza virus in the poultry population.

2: The potential for emergence of a new human strain

Whilst the H5N1 virus contains only avian genes, there is the potential that the avian strain could exchange genes with human influenza virus and generate a new strain of human influenza virus that is "antigenically shifted" from the current human strains in circulation. In order for this to occur a combination of events would need to happen before a human outbreak was possible.



An "antigenically shifted" strain of human influenza has the potential to cause a pandemic if control measures such as quarantine and vaccination cannot be applied effectively.

3: Human Vaccine Development

Laboratories in the WHO Global Influenza Surveillance Network are characterizing avian and human viruses obtained from the current outbreaks.

Preliminary results indicate that these viruses are significantly different from other H5N1 strains isolated in Asia in the recent past, thus necessitating the development of a new prototype strain for use in vaccine manufacturing. Although steps are underway to develop an influenza vaccine against H5N1, this process will take a number of months before a suitable vaccine can be tested.

The current human influenza vaccines do not provide immunity to the avian influenza virus A H5N1.

Continued inside...

Avian Influenza A strain H5N1 (continued from front page)

4: Therapy

Early studies on the effect of anti-influenza drugs on the virus have shown that the neuraminidase inhibitor class of antivirals - oseltamavir (Tamiflu) and zanamivir (Relenza) - would be the antivirals of choice in treatment.

5: Australian Environment

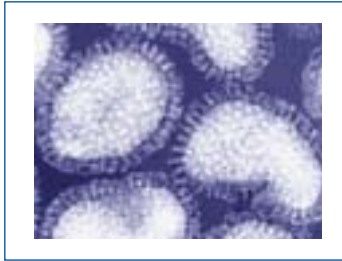
Australia is potentially at risk of imported infection via three routes:

- Breaches of quarantine
- An infected traveller
- Migrating birds from an affected area

Laboratory diagnosis of Influenza

Diagnosis of human influenza infection is best achieved by a naso pharyngeal aspirate and the specimen sent for Direct Fluorescent Antigen (DFA) testing and culture.

Positive culture specimens are then forwarded for strain identification.



Human influenza virus

Public Health

At present Australian authorities are monitoring the situation in conjunction with the WHO and other health agencies. The following Internet sites will provide current information.

Resources

The Commonwealth Health website is http://www.health.gov.au/avian_influenza/faq.htm

The WHO website is <http://www.who.int/csr/don/en>

QML's CPD Program

QML is committed to providing continuing medical education to Queensland doctors. Throughout 2004, events will be held in both metropolitan and regional areas, providing timely topics based on your feedback.

Please watch this space for details of QML's upcoming CPDs.

Topic: Women's Health Issues

CPD Pts: 4 for each of the following events:

CAIRNS

Date: **Thursday, 19th February 2004**

Venue: Cairns Private Hospital,

Time: 6:30pm for 7pm

BRISBANE NORTH

Date: **Wednesday, 17th March 2004**

Venue: TBC

Time: 6:30pm for 7pm

BRISBANE SOUTH EAST/BAYSIDE

Date: **Wednesday, 24th March 2004**

Venue: TBC

Time: 6:30pm for 7pm

Upcoming CPD locations:

Sunshine Coast

Brisbane South West

For more information or bookings please call
QML Marketing on (07) 3840 4506



Dr Anthony Watt FRCPA

Dr Watt graduated from the University of Queensland with Honours in Medicine in 1992. He commenced pathology training in 1998 and took up casual employment with QML Pathology as a registrar in the same year.

In 2003, Dr Watt was appointed full time senior registrar at QML, gaining a fellowship in anatomical pathology in September 2003.

Special Interests:

Cytopathology, Gynaecological Pathology & Gastrointestinal Pathology.

Please see important information regarding the QML Warfarin Care Clinic accompanying this newsletter.

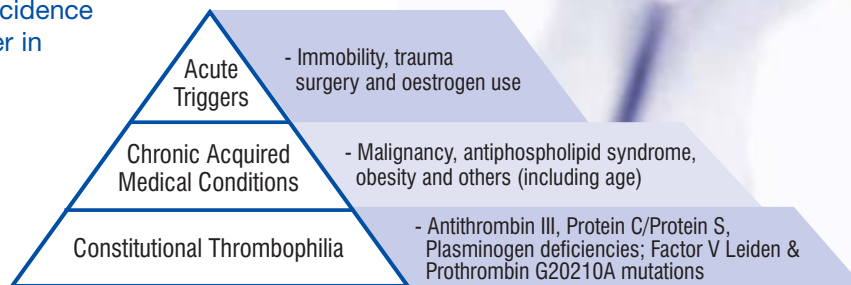
Management of LOWER LIMB DVT

by Dr Peter Davidson & Dr Sue Benson

The overall incidence of Venous Thromboembolism (VTE) is 1-2 per 1000 per year. The incidence is much lower in the young and higher in the elderly.

A thrombotic event is precipitated when events coincide or develop (like the pyramid) on top of the other. The risk factors are additive, such that when a threshold is reached a thrombosis will occur.

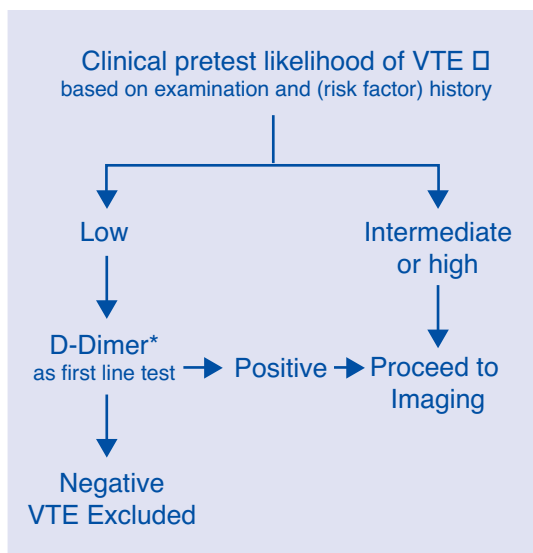
Risk factors can be stratified into the following:



DIAGNOSIS

Diagnosis of VTE can be difficult with clinical diagnosis being very inaccurate.

Clinical scoring systems in conjunction with Compression Ultrasound and D-dimer assays have allowed the design of algorithms to assist with the diagnosis.



* D-dimer assay used needs to be sufficiently sensitive and to have been validated for use in this situation. Outpatients with a low clinical likelihood of Deep Vein Thrombosis (DVT) and negative D-dimer can avoid further testing. Less than 20% of these patients will develop symptomatic DVT within 3 months.

MANAGEMENT OF PROVEN DVT

This is a two arm process:

- 1) Testing for potential underlying thrombophilic states
- 2) Treatment

1) Thrombophilia Testing

There are ongoing discussions regarding the usefulness of testing for thrombophilia in all patients who present with a first episode DVT. The aim is to identify those patients at a high risk of recurrent thrombosis and those where the results could influence management of family members. Some studies have shown that the two year cumulative recurrence rate after LMWH followed by six months of oral anticoagulants is the same as the cumulative risk of recurrent DVT due to inherited thrombophilia (10%), suggesting that testing everyone is not necessary.

It would be reasonable to test the following patient groups:

- First idiopathic or extensive DVT at age < 50
- Two (2) or more recurrent spontaneous VTEs*
- Family history with two or more first degree relatives with VTEs
- Thrombosis in an unusual site eg. Mesenteric, Portal or Cerebral vein

* It is important to distinguish true recurrent DVT, from a single episode that is slow in resolving or has organised into a chronic venous obstruction with incomplete re-canalization.

Thrombophilia screening in patients over 40 years should not be restricted to the hereditary thrombophilias. Screening for malignancy (eg. CT Abdomen) should be performed in this age group as it has been shown that up to 10% of patients with an

unexplained VTE will be diagnosed with a malignancy after the thrombotic event.

2) Treatment

The decision to treat with anticoagulants requires an assessment of:

- i) the potential benefits of anticoagulation – prevention of proximal extension or pulmonary embolism, reduction of post-phlebotic complications

AND

- ii) the potential risks of anticoagulation – namely bleeding/haemorrhage.

Bleeding risks are increased with:

- age (>65)
- renal disease
- liver disease
- diabetes
- previous stroke
- gastrointestinal bleeding
- malignancy.

With standard-intensity therapy (target INR 2-3):

- 5-15% experience minor bleeding
- 2-3% experience major bleeding
- 0.2-0.6% experience fatal bleeding each year

In tailoring an anticoagulation plan the following points are important:

Assessment of the anticoagulation benefit/risk to allow the following to be determined

- Anticoagulation intensity (eg. INR target range)
- Minimum duration of treatment

AND

- Risk Recurrence Assessment – based on thrombophilic risk factor assessment. (see below risk recurrence)

Lower limb DVT confined below the knee crease (ie. Calf DVT) is well known to be less likely to extend or embolise. Proximal extension risk is 5-10% and the Extension Risk Period is within the first 14 days.

Thus, formal anticoagulation may not be needed in low-risk calf DVTs.

FORMAL ANTICOAGULATION

(a) Initial anticoagulation

This is usually heparin based. Thrombolytic therapy is not routinely used.

Low molecular weight heparin (LMWH) has replaced unfractionated heparin (UFH) as the drug of choice. LMWH has been shown to be as effective as UFH in the initial treatment of lower limb VTE with the advantages of subcutaneous route, weight adjusted dose and monitoring is not required.

The large majority of patients with a first DVT can be treated as outpatients.

Two LMWH drugs are available:

- Enoxaparine (Clexane) may be given as a
 - once daily dose of 1.5mg/kg body weight
 - twice daily dose of 1mg/kg body weight
- Dalteparin sodium (Fragmin) given as twice daily dose of 100IU/kg body weight

The drugs are not interchangeable with respect to their activity.

Disadvantages of the drugs in comparison to UFH include a less predictable response with morbid obesity, advanced renal disease and pregnancy. Monitoring requires the more complex anti-Xa test and reversal of the drug effect cannot be completely achieved with protamine sulphate.

Treatment with LMWH is needed for at least five days and until a therapeutic affect has been achieved with the oral anticoagulant.

(b) Long term phase

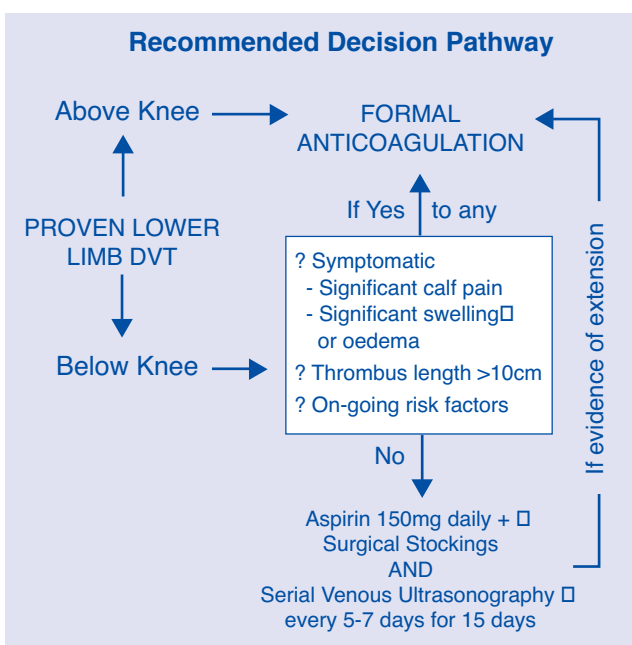
After initial treatment with LMWH, oral anticoagulant (OAC) therapy needs to continue to prevent thrombotic complications or acute recurrence.

The coumarin derivative warfarin is the usual OAC and may be commenced on the same day as LMWH.

The standard starting regime is 5mg daily but smaller doses are required for elderly, frail and patients of low body weight. The dose is monitored by INR measurement initially every two to three days with the aim of achieving the therapeutic range of 2-3 within four to five days. LMWH is continued until the INR has been at least 2.0 for two days.

The testing period can be extended as INR stability is reached from twice weekly to weekly and longer periods. Patients who are stable and who have a good understanding of their therapy may only need testing at 10-12 weekly intervals.

Warfarin is a drug that is notorious for problems. There is a narrow therapeutic window and frequent monitoring may be required. Drugs, diet, alcohol,



exercise and intercurrent illness can all interfere with the effect of warfarin. Most studies show that less than 60% of patients are in the therapeutic range at any one time.

c) Completion

As noted above, how long a patient needs to remain on warfarin requires an assessment of the risks of warfarin therapy versus the risks of a VTE progression and the risk of it likely to recur.

Thrombotic events may be stratified into risk categories for recurrence depending on the nature of the event and patient factors.

Risk Recurrence

Low risk: risk of recurrence <5%

- Provoked VTE with reversible risk factor eg. surgery, trauma, immobilisation, estrogen therapy
- Isolated distal DVT

Moderate Risk: risk of recurrence 5-10%

- First idiopathic VTE
- Spontaneous VTE with heterozygous Factor V Leiden or Prothrombin G20210A mutation

High Risk: risk of recurrence >10%

- Recurrent unprovoked VTEs with or without identifiable thrombophilia
- First spontaneous VTE with Antithrombin III, Protein C or Protein S deficiency; homozygous Factor V Leiden; double heterozygosity; antiphospholipid syndrome
- Active malignancy

The major risk of warfarin is bleeding. The major risk of recurrent VTE is death due to PE which occurs in 5% of patients with a recurrent thrombosis. If the annual rate of recurrent VTE is 12%, the risk of death from recurrent thrombosis is balanced by the risk of death from bleeding.

Recommended Completion Dates

Risk	INR Target	Standard Duration	Maximum Duration
Low	2.0-3.0	6-12 weeks	
Moderate	2.0-3.5	6-12 months	
High	2.5-4.0	12-24 months	Indefinite

Thrombus that has proximal involvement should be treated for a period and at an intensity at the higher end of the range.

At the finish of the standard period of anticoagulation, decisions need to be made regarding anticoagulation:

- Should anticoagulation be ceased
- Should full anticoagulation continue or
- Should low intensity anticoagulation be instituted.

To aid in this decision the patient should be reviewed, and probably the venous ultrasound should be repeated to determine extent of resolution, and possibly a D-Dimer titre performed.

The presence of residual thrombus or the persistence of D-Dimer suggests that anticoagulation should continue in some form for another standard interval. The presence of on-going risk factors may also determine whether anticoagulation should continue.

Alternatives to Standard Anticoagulation

Warfarin is associated with unwanted bleeding, requires ongoing monitoring and has interactions with a wide variety of drugs and conditions. It can be very difficult to maintain some patients in the therapeutic range. LMWH has been shown to have similar rates of thrombosis and major bleeding as standard OAC and does not require laboratory testing. It is thought to be more effective than warfarin in patients with cancer associated thrombosis and those with recurrent thrombosis whilst on warfarin. Its disadvantages include cost and the need for parenteral administration but patients with advanced malignancy who require aggressive chemotherapy may benefit from its use.

References:

- How we diagnose and treat deep vein thrombosis, Hirsh and Lee, *Blood*, 1 May 2002: 3102-3110
- Long term management of venous thromboembolism, Eikelboom and Hankey, *MJA*, 21 July 2003: 68-69
- Unresolved issues in anticoagulation therapy, Schulman J., *Thromb Haemost*, July 2003: 1464-1470
- Incidence of recurrent VTE in relation to clinical and thrombophilic risk factors, Baglin et al, *Lancet*, 16 August 2003: 523-526



Ballina Lab provides support for Northern Rivers

QML Pathology now has a laboratory facility at Ballina, providing a dedicated diagnostic service for the Tweed, Lismore & Northern Rivers region. The Ballina laboratory has on-site testing facilities and highly-trained scientific staff able to perform routine tests in the following disciplines:

- Biochemistry
- Haematology
- Microbiology
- Endocrinology

QML's courier network services all medical practices, nursing homes and Veterinary practices throughout the region, encompassing Byron Bay to Lismore and surrounding areas.

To ensure a more personalised service and faster turn around time for pathology requests, QML Ballina is supervised by consultant pathologist, Dr Glenn Francis, with additional support from the Southport and West End laboratories provided for more complex tests.

COLLECTION CENTRES

Ballina		(02) 6686 6424
46 Tamar St (entry via Moon St)	Mon-Fri Sat	7.30am – 5.30pm 8.00am – 11.00am
Lismore		(02) 6621 4488
69 Uralba St	Mon-Fri	8.00am – 1.00pm 1.30pm – 4.30pm
Byron Bay		(02) 6685 6681
52 Shirley St	Mon-Fri	8.30am – 1.00pm 2.00pm – 5.00pm



Doctors' Notice Board

Dr Malcolm Frazer, Gynaecologist/Urogynaecologist, would like to advise of a change of address effective January 2004. Dr Frazer is now consulting at 156 Ashmore Rd, Benowa. For appointments and consultations please telephone (07) 5564 9300, mobile 0404 072 038 or facsimile (07) 5597 6686.

Dr Josephine Cheung, Obstetrician/ Gynaecologist, is now consulting at both Mater Private and North West Private Hospitals. Dr Cheung is fluent in Cantonese and conversant in Mandarin. For enquiries and appointments please telephone (07) 3010 3322.

Dr Robyn Boston FRANZCOG, is commencing part-time Gynaecology practice from February at the Bowman Centre, Caloundra. Dr Boston specialises in pelvic floor dysfunction – diagnosis and management. For all enquiries, please telephone (07) 5499 7366.

COLLECTION CENTRE NEWS

Correction: The QML Toowoomba telephone number was printed incorrectly in the previous edition of the QML Newsletter. We apologise for any inconvenience this may have caused. Please find the correct details listed below:

Toowoomba		(07) 4633 0729
Shop 6A, Wilsonton Shopping Centre, 407 Bridge St	Mon-Fri Sat	7.30am – 4.30pm 8.00am – 10.30am

NEW COLLECTION CENTRES

Woodlands		(07) 4751 6879
Shop E, Woodlands Shopping Centre Palm Drive, Deeragun	Mon-Fri Sat	8.00am – 1.00pm 2.00pm – 4.30pm 8.00am – 12.00noon

NEW OPENING HOURS

Gympie		(07) 5482 7577
Cooloola Specialist & Diagnostic Centre 74 – 76 Channon St	Mon-Fri Sat	8.00am – 5.00pm 9.00am – 11.30am
Maryborough		(07) 4123 6615
2/275 Kent St	Mon - Fri Sat	8:00am – 5.00pm 9:00am – 11.00am

Please contact your local branch or Brisbane Liaison for further information on (07) 3840 4539.



Mayne Health Pathology Pty Ltd ABN 84 007 190 043 t/a Queensland Medical Laboratory

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MAR/PUB/11/0204