The Use of Semi-permanent Central Venous Catheters in a Population of Hospital Patients with Malignant Disease: Determinants of Adverse Outcomes

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January, 1995

A subthesis submitted (or submitted in partial fulfilment) for the degree of Master of Population Health of the Australian National University.
The sub-thesis is entirely my own work with the exception of some data extraction from medical records performed by Dr A. Dorrigo and Ms J. May (Medical Oncology Department, Woden Valley Hospital) and measurements taken from chest radiographs performed by Dr C. Hoy (Department of Radiology, Woden Valley Hospital). These aspects of the project were performed under my supervision.

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1. INTRODUCTION: TRENDS IN CANCER CONTROL

The Australian population experiences a lifetime risk of cancer (excluding non-melanocytic skin cancers) to age 75 of about 1 in 4. Cancer is the second most common cause of death, after circulatory disease. In 1992, in Australia, 32,003 deaths due to cancer were registered, representing 26% of all deaths (Australian Institute of Health & Welfare, 1992). Crude incidence and mortality rates of cancer have risen in Australia over the past 3 decades. Much of this increase is due to the increasing age of the Australian population (National Goals and Targets Report, 1994).

Although crude cancer mortality rates increased between 1985 and 1992, the age standardised mortality rate from cancer actually fell by about 5%. There has also been a consistent improvement in cancer case survival rates over the past 14 years observed in South Australia, where these data are available (SA Health Commission, 1994). It would seem reasonable to assume the same trend would be followed throughout the remainder of Australia. Similar changes in case survival rates have been reported from the United States (Boring et al., 1992).

The large burden of morbidity and mortality endured by the community due to cancer has lead to the identification of cancer control as a priority health issue in Australia (National Goals and Targets Report, 1994). The aetiology of a number of important cancers is clearly associated with environmental and lifestyle factors such as smoking. A major goal will remain primary prevention through behaviour modification and environmental control. Secondary prevention requires the early diagnosis of malignant or pre-malignant lesions. Screening programs have been extended for cancers, such as breast cancer, where these programs are useful. Despite these initiatives, cancer incidence is projected to rise further. Ever increasing numbers of patients with cancer can be expected to present for care and treatment. Thus, improvements in cancer therapy are needed to increase cancer control rates. Some of these improvements may help to contain the economic cost of the disease. Improved cancer treatment, and particularly improvement in the associated supportive care, is central to maintaining the quality of life of people who develop cancer. As will be discussed, safe and simple methods of obtaining repeated access to the circulatory system of patients under clinical care have become crucial in permitting optimal cancer care.
2. THE INCREASING REQUIREMENT FOR VASCULAR ACCESS

Cancer survival rates have slowly improved over the past 20 years. The factors underlying this improvement are difficult to measure, however improved outcomes from medical treatment are likely to be important. Improved and earlier diagnosis is also likely to be important. Approximately 60% of internal malignancies are cured with currently available therapeutic interventions. Modern cancer care incorporates the use of the three main modalities of cancer treatment, that is, surgery, radiotherapy and chemotherapy often in a combined approach.

Vascular Access in Cancer Surgery and Radiotherapy

Developments in surgical practice have enabled more effective cancer surgery to be performed with less morbidity. As the scope of new surgical techniques in fields such as reconstructive surgery have developed, the complexity of the requisite supportive care has increased. This supportive care is essential in permitting new surgical treatments to be successfully applied. Prolonged intravenous access is a feature of the intensive care which supports the surgical patient with cancer. The efficacy of parental nutrition in preventing surgical complications in patients undergoing surgery for advanced cancer is well established. Semi-permanent central venous catheters are an essential component of most parenteral nutrition programs.

In radiotherapeutic practice the development of infusional schedules of 5-flourouracil, cisplatin, and other chemotherapeutic drugs which may act as radio-sensitising agents has been an increasingly applied technique (Sugarbaker et al., 1985). The concomitant infusion of 5-flourouracil with radiotherapy has been shown to improve response rates, compared to radiotherapy alone, in the treatment of carcinoma of the cervix, anal canal, and oesophagus. Active investigation of this approach is continuing and the application of this and similar forms of treatment is likely to expand as efficacy is demonstrated (for example Leichman et al., 1993). Such combined modality programs need prolonged and durable venous access. Semi-permanent central venous catheters have facilitated the development of this therapeutic approach.
Chemotherapy and Vascular Access

Since the initial trial of nitrogen mustard chemotherapy for Hodgkin's disease in 1943 more than 30 anti-cancer cytotoxic agents have entered regular clinical use. It has been estimated that more than 250,000 people with cancer are treated annually in the United States with cytotoxic chemotherapy (DeVita 1985). Almost all of this treatment is given by injection, usually by intravenous infusion. Providing the means for physically administering this therapy as well as providing a route to facilitate the associated supportive care has lead to a steady increase in the use of semi-permanent intravenous devices.

Continuing attempts are being made to maximise the cancer control rate with the currently available chemotherapeutic drugs. Strategies have included the use of combinations of drugs to take advantage of possible synergism and to prevent the development of tumour cell resistance (Scanlon & Nee Dels, 1986). More complex drug combinations and schedules, and the associated supportive treatment, transfusions and antibiotics, have led to the more frequent use of semi-permanent catheters. A steady increase in the frequency of Hickman catheters in patients with predominantly haematological malignancy has been reported from an Australian hospital over a recent 7 year period (Gibson et al., 1994).

More recently the relationship between dose intensity and control rates have been examined. Higher dose intensity has been associated with better control rates in studies of breast cancer, lymphoma, and acute leukaemia (Hryniuk et al., 1986). Dose intensity may be increased with the application of intensive supportive care such as autologous peripheral stem cell infusions.

Autologous bone marrow transplantation and the related procedure of autologous peripheral stem cell infusion are methods allowing the use of very dose intense chemotherapy. Patients undergoing these procedures require intensive supportive care. Semi-permanent central venous catheters are universally required for these procedures. The final place these forms of treatment will have in the management of common haematological and solid malignancies remains unclear, however 333 autologous bone marrow transplants were performed in Australia in 1993 (Atkinson & Szer, 1994). Semi-permanent central venous catheters may be used both for the
cytophoresis procedure where peripheral blood stem cells are collected and for the high dose chemotherapy and related supportive care.

Allogeneic bone transplantation is now an established treatment for various forms of leukaemia and other haematological disorders. The number of transplants performed world wide has risen steadily to over 5000 per year in 1990 (Borton et al., 1992). Such procedures lead to the requirement for a prolonged period of very intensive supportive care during which semi-permanent central venous catheters are ubiquitous. The insertion of some form of central venous catheter is mandatory in most transplantation centres at the beginning of the procedure (Flowers & Sullivan, 1994).

Continuous Infusional Chemotherapy

The administration of cytotoxic chemotherapeutic drugs as a continuous slow intravenous infusion has been developed as a way of increasing dose intensity and efficacy. Cytotoxic drugs that are cell-cycle phase-specific in their action are suitable for this approach, particularly if they have a short terminal half-life.

Some cytotoxic drugs, such as 5-fluorouracil are clearly more efficacious in treating certain cancers, such as breast cancer, when given as a slow infusion (Anderson 1993). The use of continuous infusions of 5-fluorouracil in ambulatory patients has become feasible because of the availability of reliable semi-permanent catheter systems such as Hickman catheters (for example Jones et al., 1994). When used in this way, 5-fluorouracil is less myelosuppressive, and other forms of toxicity such as mucositis or diarrhoea become the dose limiting factors. Much higher dose rates are achievable with continuous infusions compared to conventional bolus administration (reviewed by Hansen, 1991).

An improved therapeutic index for slow infusional chemotherapy has been reported for bleomycin (Remick et al., 1994). Other cytotoxic drugs which may beneficially be administered as prolonged infusions include doxorubicin, cisplatin, and vinblastine. Many of the cytotoxic drugs currently being administered by slow continuous infusion are dangerous if extravasated. As with radiation sensitisers and bone marrow transplantation, the widespread inclusion of infusional therapy into therapeutic protocols has only become feasible because of the availability of safe methods of obtaining durable access to the central circulation.
Economic Issues and Venous Access

The development of moderately efficacious but ever more complex cancer treatment has had major cost implications. As supportive care has improved, complex therapeutic protocols have been able to be safely administered to a wider group of patients with cancer. The general application of what were once considered to be highly specialised investigational therapies will have continuing economic repercussions. While semi-permanent central catheters have had a permissive role in the penetration of these new complex protocols into more general clinical use, they may also provide a means of reducing cost in certain circumstances.

More robust methods of obtaining durable venous access have been important in permitting the transfer of an increasing proportion of care to the clinic and out of hospital wards. Patients with a semi-permanent central venous catheter, such as a Hickman catheter, in situ may have intravenous infusions and catheter care provided at home. Continuous intravenous infusions of cytotoxic drugs are routinely given through central venous catheters using a miniature pump worn or carried by ambulant patients at home. People requiring prolonged parenteral nutrition or intravenous antibiotic therapy are able to be given this therapy at home via a semi-permanent central venous catheter (Pomp et al., 1989; Mukau et al., 1992).

The provision of intravenous therapy outside of traditional hospital facilities may represent an important improvement. The avoidance of hospital admissions for infusions improves the quality of life for the patients involved. A reduction in the number of hospital admissions would be expected to have economic benefits in terms of cost per patient cared for, depending on the cost structure of the health system in question. Studies are under way in Australia to assess the economic impact of home infusion chemotherapy programs (Prof R Kefford, personal communication).
3. STUDY OF HICKMAN CATHETER USE IN WODEN VALLEY HOSPITAL: AIMS AND OBJECTIVES

Aims

To examine the pattern of use, duration of use and adverse events associated with use of Hickman catheters in the study population.

To explore the determinants of adverse events associated with Hickman catheter use within the study population.

Primary Objectives

To develop a predictive model for the risk of Hickman catheter failure as defined by removal of the catheter because of a complication.

To explore the determinants of catheter malfunction (as defined) with particular reference to the measured catheter tip position, the site of insertion, duration of catheter use, and the patient diagnostic group.

Secondary Objectives

To explore the determinants of Hickman catheter infection within the study population.

To explore the determinants of Hickman catheter migration or dislodgement within the study population.
4. REVIEW OF METHODS FOR OBTAINING AND MAINTAINING VENOUS ACCESS

In this section an overview of methods in current practice for obtaining venous access is provided. Methods described include the simple peripheral intravenous cannula, non tunnelled central venous catheters, the tunnelled central venous catheters such as the Hickman and Groshong, and fully implanted subcutaneous ports. Different techniques of insertion of Hickman catheters are also discussed.

Peripheral Venous Catheters

Venous access has been traditionally obtained via peripheral veins using steel needles or polyethylene intravenous cannulas. Modern steel scalp vein needles continue to be used for short term venous access. Peripheral vein plastic cannulas are ubiquitous within hospital facilities in developed countries. These peripherally inserted cannulas are cheap and easy to insert. While ideal for short term use, peripheral venous catheters have many limitations. They are unsuitable for use with continuous infusions of irritant solutions, such as some anti cancer cytotoxic drugs, and parenteral nutrition infusate. Attempted infusion of such fluids into a small peripheral vein (with relatively low blood flow) causes local phlebitis. Peripheral vein cannulas frequently block or kink. The tip of the cannula can migrate to an extravascular site. The accidental infusion of some drugs, formulated for intravenous use, into the subcutaneous tissues due to a malfunctioning peripheral cannula (i.e. accidental extravasation) can lead to loss of efficacy and local toxicity. Extravasation of some cytotoxic drugs can lead to catastrophic local toxicity with tissue necrosis and tendon loss (de Fraine et al., 1990).

Peripheral cannulas must be changed frequently, even when meticulously cared for, in order to reduce the risk of infection to acceptable levels (Simmons 1983). Infectious complications from these cannulas are a major source of iatrogenic morbidity within hospitals (Arnow et al., 1993). Because of the very large number of peripheral cannulas used, complications, particularly nosocomial infection, are a major health issue for hospital practice. Intravenous therapy nursing teams and other interventions aimed at reducing this morbidity have been instituted in a minority of hospitals in Australia, and may be cost effective (Collignon et al., 1985). A similar benefit
from dedicated nursing teams has been observed elsewhere (Weightman et al., 1988; Gianino et al., 1992).

Non-tunnelled Central Venous Catheters

When parenteral nutrition and other intensive supportive care methods entered widespread use between 1960 and 1970, techniques for inserting and maintaining polyethylene central venous catheters, inserted via subclavian or jugular veins, were developed. Nosocomial infection occurring in these critically ill patients related to the central venous catheter were frequently encountered (Maki et al., 1973). To reduce this risk polyethylene central venous catheters have been replaced every 7 to 10 days (Daly et al., 1981). Catheters which are "tunnelled" subcutaneously before entering a vein were developed to address the problem of nosocomial catheter related infection, allowing the long term use of a single catheter.

Recently non-tunnelled silicone rubber central venous catheters have been developed for long term use. These catheters are cheaper to insert than the tunnelled silastic catheters described below (Raad et al., 1993A). They are either inserted into the subclavian vein or peripherally inserted in the antecubital fossa and advanced intraluminally into the central circulation (the so-called peripherally inserted central catheters or PICCs). When inserted and cared for by a dedicated hospital infusion therapy team, they have proved to be reasonably durable with complication rates comparable to those of tunnelled catheters (Slater et al., 1985; Raad et al., 1993A).

Tunneled Silicone Rubber Central Venous Lines (Hickman or Broviac Catheters)

In 1973 the use of a tunnelled silicone rubber right atrial catheter was developed by Broviac et al. in an attempt to reduce infectious complications (Broviac et al., 1973). This catheter was placed surgically, usually by a "cut down" to the cephalic vein. It was used primarily for parenteral nutrition (Heimbach & Ivey 1976). The small internal diameter of the catheters used (0.22 mm) did not allow for the infusion of thicker fluids such as blood products or for the easy withdrawal of blood for pathological testing.

An improvement of this catheter, designed for use in adults, and in particular adults with malignant disease, was described in 1979 by Hickman (Hickman et al., 1979). This catheter, like the Broviac catheter was made of silicone
rubber, but was larger with a slightly thicker wall and a larger internal
diameter of 0.32 mm. These catheters have achieved very wide use
internationally and arguably represent the current standard method of
obtaining durable intravenous access in patients receiving cancer treatment
(Reed et al., 1989). A benefit from catheter tunnelling, in terms of reduced
catheter related sepsis, has been demonstrated in a single small randomised
trial (Keohane et al., 1983). In this study, the benefit of catheter tunnelling
was apparent only when nursing care of the catheters may have been sub
optimal.

**Methods of Hickman Catheter Insertion**

**Surgical Open Insertion**

When originally developed, Broviac and Hickman catheters were inserted
surgically in an operating theatre under local or general anaesthesia.
Typically, either the cephalic or internal jugular veins were isolated and the
catheter inserted through a small incision in the vein wall. The catheter tip
was advanced, under fluoroscopic control in Hickman's series, to the lower
superior vena cava where it enters the right atrium. The vein wall was closed
with a suture. Both left and right sided approaches were used. A
subcutaneous tunnel was fashioned from the vein entry point to an exit site
on the anterior chest wall. Several centimetres from the exit site a Dacron
felt cuff surrounded the catheter, anchoring it, and also (presumably) forming
a barrier against infection. Thus the features of Hickman and Broviac
catheters which were novel in 1979 were the silicone rubber material rather
than the usual polyethylene, the subcutaneous catheter tunnel, and the
Dacron felt cuff proximal to the exit site. It was believed that these features
were likely to reduce the risk of infection and allow for long term use of the
catheter (Hickman et al., 1979). Both types of catheter continue to be widely
used (Press et al., 1984). The smaller Broviac catheter has been used
mainly within paediatric populations and the larger Hickman catheter in both
children and adults (Mirro et al., 1989).

**Percutaneous Insertion of Hickman Catheters**

Insertion of these catheters into the central circulation by directly puncturing
the left or right subclavian or jugular vein, using a Seldinger technique, is an
alternative now in wide use (Mirro et al., 1990; Wisborg et al., 1991; Hughes
et al., 1989; Kirkemo & Johnston 1982; Shulman 1982). The technique has
the advantage of not necessarily requiring the use of operating theatre facilities, as an open dissection of a vein in the neck is not performed.

Percutaneous Hickman catheter insertion can be performed, under aseptic conditions, within an angiographic suite, using local anaesthesia (Page et al., 1990; Robertson et al., 1989). Visualisation of the subclavian vein radiographically by performing arm venography prior to catheter insertion has been employed (Cockburn et al., 1992). This allows for a secure approach to vein puncture and can reduce the risk of accidental arterial puncture and bleeding. Moreover, unexpected subclavian vein thrombosis or stenosis may be detected before catheter insertion is attempted, allowing the selection of an alternative method of obtaining venous access. As the catheter is placed, under fluoroscopic control, any gross malposition of the catheter tip may be corrected (Page et al., 1990). However the exact position of the catheter tip is not known until the patient adopts an erect posture after the procedure. Immediate complications, such as haemothorax or pneumothorax, can be detected by performing a post insertion radiograph.

Similar methodology has been developed using ultrasound to provide sonographic guided puncture of the subclavian vein (Lameris et al., 1990). Duplex Doppler ultrasound has been used to examine flow patterns within the jugular and subclavian veins, allowing the identification of thrombosed or stenosed veins unsuitable for catheter insertion (Kraybill & Allen, 1993; McIntyre et al., 1992).

Hickman catheters have been successfully placed in the inferior vena cava with insertion via the femoral vein in circumstances where conventional placement in the superior vena cava was impossible (Kohli-Kumar et al., 1992; Williard et al., 1991).

Percutaneous insertion of Hickman catheters using a Seldinger technique has some potential disadvantages when compared to the surgical cut-down method. These include the possibility of catheter compression and breakage as it passes between the clavicle and first rib (Hinke et al., 1990). There is also a putative increase in the risk of extravasation of infused drugs from the catheter due to catheter encasement in a fibrin sheath (see section 4) (Reed et al., 1989; Glemlo et al., 1988). These complications have been infrequently reported.
Other Tunneled Catheters - The Groshong Catheter

The Groshong catheter is a silicone rubber catheter of similar design to the Hickman catheter. It differs only in that it has a pressure sensitive two-way valve at the intravascular tip which prevents the entry of blood into the catheter unless negative pressure is applied by aspirating with a syringe to withdraw blood (Malviya et al., 1989). The design is aimed to reduce retrograde entry of blood into the catheter and therefore the need for routine flushing. Non-randomised comparisons have not shown measurable advantages over Hickman catheters (Pasquale et al., 1992; Davidson et al., 1988).

Fully Implanted Catheter Systems - "Ports"

Hickman catheters have a permanent skin exit site which may provide a portal for entry of pathogens. The catheter exit site requires regular dressings. The external portion of the catheter can suffer accidental traction, causing catheter dislodgement. Hickman catheters have obvious cosmetic problems, particularly for children. In order to overcome these disadvantages, fully implantable access devices or ports were developed (Strum et al., 1986). The port consists of a metal injection chamber connected to a silicone rubber outlet catheter. The chamber can be punctured through a self sealing membrane of silicone rubber, using especially designed non traumatising needles. The catheters are inserted into a central vein and then connected to the port which is implanted subcutaneously. The membrane is punctured directly through the skin to obtain central venous access (Reed et al., 1989).

These devices have been shown in non-randomised studies to have a lower risk of infectious complications (Mirro et al., 1990; Ross et al., 1988). In a retrospective matched cohort study, Peques et al. demonstrated a reduced infection rate and time to first infection for implanted ports compared to Hickman catheters in adults with solid malignancies (Pegues et al., 1992).

Three small prospective randomised trials comparing Hickman catheters to fully implanted ports in patients with cancer have been reported (Kappers-Klunne et al., 1989; Carde et al., 1989; Mueller et al., 1992). In the study by Mueller et al., a total of 100 patients with varying forms of malignant disease were randomised to have either a Hickman catheter or a port inserted. Ninety-two patients were assessable. There were more episodes of
unexplained fever in the implanted port group but no difference in the complication rate overall between the two groups. There was no difference in the rates of thrombotic complications. A similar study by Kappers-Klunne et al. in 44 patients with haematological malignancy also did not show any difference in infection rates. The third study by Carde et al., performed in 100 patients with solid tumours requiring at least 6 months venous access, showed an prolonged time to device failure for the implanted port group compared to Hickman catheters. The excess in Hickman catheter loss was due to catheter dislodgement and to a lesser degree, infection.

The successful use of fully implanted ports has been reported in paediatric and adult cancer patients and in AIDS patients (Essex-Cater et al., 1989; van der Pijl & Frissen 1992). These ports have also been used to provide parenteral nutrition (Pomp et al., 1989). These devices are somewhat more difficult to implant, particularly in patients with haematological disease when post-operative bleeding can occur, and they are costly to insert, in relation to Hickman catheters. Hickman catheters are however, more expensive to maintain. The relative cost-effectiveness of these devices has not been elucidated. Fully implantable ports have been more readily accepted by children than Hickman catheters (Ross et al., 1988).

Other Methods of Obtaining Vascular Access

Other strategies used to obtain durable vascular access have included the use of surgically fashioned arteriovenous fistulae (Reed et al., 1982). Arteriovenous fistulae have not been popular for patients requiring chemotherapy, but are widely used for chronic haemodialysis (Reed et al., 1989). Thrombosis and blockage are frequent problems. Hickman catheters were preferred in a comparative study with arteriovenous fistulae in patients with acute leukaemia (Wade et al., 1981).

Summary

Hickman catheters are currently the most widely used devices for obtaining and maintaining access to the central circulation in adults with cancer. Fully implantable ports are a reasonable alternative for patients without severe thrombocytopenia or coagulopathy at presentation. Further alternatives include the use of silicone rubber non-tunelled central catheters or the use of peripherally inserted central catheters.
5. HICKMAN CATHETER USE: OUTCOMES AND ADVERSE EVENTS

As discussed in section 4, Hickman catheters have been widely used in clinical circumstances where prolonged venous access is required. Settings where these catheters continue to be used include chronic haemodialysis, total parenteral nutrition, and cancer treatment. Their use has facilitated the development of ambulatory outpatient treatment programs and more recently home infusional programs (Mukau et al., 1992). In this section the reported experience of Hickman catheter use and associated adverse events is reviewed.

Selected studies describing the use and related adverse events of Hickman catheters are listed in table 1. Most of these observational studies have included, within the study cohort, ambulatory subjects for whom some of the catheter care has been performed at home. The median duration of catheter use in these studies ranges from 30 days up to 365 days. The large majority of catheters have been used without major problems and then removed electively when no longer required, although in one study 41% of catheters were removed because of complications (Haywood et al., 1990).

Hickman catheters have been well accepted by patients who appreciate the ease of vascular access and the avoidance of repeated venipuncture and needle phobia (Claessen et al., 1990). Fully implantable ports may be preferred particularly by children requiring repeated intravenous access (Ross et al., 1988).

While the use of Hickman catheters has been an innovation in cancer medicine, their widespread introduction has been accompanied by significant adverse events and attendant morbidity. Complications reported in relation to Hickman catheter use include, in descending order of frequency: infection, central venous thrombosis, catheter blockage, catheter migration or dislodgement, mechanical failure or fracture, and extravasation of infused fluids. Acute complications of catheter insertion such as pneumothorax and bleeding can occur. Some rare adverse events have been reported as case reports. The successful use of these devices requires the development of strategies to minimise the incidence of complications and to ameliorate the impact of complications which do occur. The most important complications of Hickman catheter use are discussed.
Table 1
Hickman Catheter Failure Rate and Duration Of Use

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Clinical Setting</th>
<th>Median Duration of Use in Days</th>
<th>Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hickman et al., 1979</td>
<td>74</td>
<td>Bone Marrow Transplantation</td>
<td>NR</td>
<td>30%</td>
</tr>
<tr>
<td>Reed et al., 1983</td>
<td>106</td>
<td>Adult Malignant Disease</td>
<td>108</td>
<td>10%</td>
</tr>
<tr>
<td>Press et al., 1984</td>
<td>129</td>
<td>Adult Acute Non-lymphocytic Leukaemia</td>
<td>128*</td>
<td>19%</td>
</tr>
<tr>
<td>Harvey et al., 1986</td>
<td>77</td>
<td>Haematological Malignancy</td>
<td>77</td>
<td>19%</td>
</tr>
<tr>
<td>Al-Sibai MB et al., 1987</td>
<td>160</td>
<td>Adult Malignant Disease</td>
<td>131*</td>
<td>23%</td>
</tr>
<tr>
<td>Ross et al., 1988</td>
<td>41</td>
<td>Paediatric Malignancy</td>
<td>365</td>
<td>32%</td>
</tr>
<tr>
<td>Hughes et al., 1989</td>
<td>342</td>
<td>Adult Malignant and Non Malignant</td>
<td>30</td>
<td>31%</td>
</tr>
<tr>
<td>Raviglione et al., 1989</td>
<td>71</td>
<td>Adult Malignant Disease and AIDS</td>
<td>76*</td>
<td>17%</td>
</tr>
<tr>
<td>Claessen et al., 1990</td>
<td>120</td>
<td>Adult Malignant Disease</td>
<td>96</td>
<td>21%</td>
</tr>
<tr>
<td>Hayward et al., 1990</td>
<td>100</td>
<td>Adult Malignant Disease</td>
<td>NR</td>
<td>41%</td>
</tr>
<tr>
<td>Mirro et al., 1990</td>
<td>266</td>
<td>Paediatric Malignancy</td>
<td>NR</td>
<td>24%</td>
</tr>
<tr>
<td>Mueller et al., 1992</td>
<td>46</td>
<td>Adult Malignant Disease</td>
<td>230*</td>
<td>17%</td>
</tr>
<tr>
<td>Mukau et al., 1992</td>
<td>140</td>
<td>Adult AIDS and Other</td>
<td>129*</td>
<td>26%</td>
</tr>
<tr>
<td>Rizzari et al., 1992</td>
<td>135</td>
<td>Paediatric Malignancy</td>
<td>152*</td>
<td>11%</td>
</tr>
<tr>
<td>Uderzo et al., 1992</td>
<td>55</td>
<td>Paediatric BMT</td>
<td>111</td>
<td>16%</td>
</tr>
</tbody>
</table>

NR = Not Reported; * = mean
Hickman Catheter Related Infection

Infection remains the most important problem associated with the long term use of Hickman catheters. The presence of a semi-permanent central venous catheter has been shown by von Hoff et al., (1990) to be a major risk factor for bacteraemia in children receiving chemotherapy. In their retrospective cohort study of children receiving chemotherapy in a single institution, those children with central venous catheters (Hickman or Broviac catheters) experienced a risk of infection 6.4-times that of children without catheters after controlling for other risk factors in a logistic regression model. These investigators found that children with central venous catheters spent an average of 15.4 more days per year in hospital for the treatment of catheter related complications, mostly infections.

In a retrospective, matched case control study conducted in a large adult hospital, the presence of a Hickman catheter was a major risk factor for the development of nosocomial candidaemia, with an estimated odds ratio of 7.23 (Wey et al, 1989). Other identified risk factors for candidaemia in this study were: treatment with multiple antibiotics, prior haemodialysis, and the isolation of Candida species from other sites. Karabinis et al., (1988) have reported a retrospective case-control study in adult patients with cancer examining the determinants of candidaemia. Central venous catheters were a significant risk factor for candidaemia with a matched relative risk of 6 in this study when estimated using a logistic regression model.

Decker & Edwards (1988) have nominated intravascular catheter related infection as the major form of nosocomial infection in United States hospitals. It has been estimated that over 170,000 cases of nosocomial bacteraemia occur annually in the United States and that 50,000 of these are due to some form of intravascular catheter (Bryan et al., 1986). Collignon (1994), has recently documented the extent of nosocomial sepsis related to central venous catheters in Australia. He has estimated the rate of central venous catheter sepsis as 5.5 infections per bed year or 23 infections per 1000 catheters purchased by the hospitals surveyed.
Pathogenesis of Catheter Infection

Direct access to the circulation provides an easy portal of entry for organisms, bypassing the physical barriers to infection. Frequent use of the catheter for intravenous infusions, irrigations to prevent clotting in the catheter and blood sampling might increase access of pathogenic organisms. Body movements can facilitate the migration of organisms along the external surface of the tunneled portion of the catheter, eventually reaching the circulation.

Bacterial Biofilms:
Intravascular catheters are known to develop bacterial biofilms of slime or glycocalyx, in which colonising bacteria, usually *Staphylococcus epidermidis*, may be observed using electron microscopy (Newman *et al.*, 1993). Such biofilms are almost universally present, even on catheters in situ for only 1 day (Passerini *et al.*, 1992). In long term catheters, the colonisation is on the luminal surface (Raad *et al.*, 1993B). The significance of biofilms and bacterial colonisation of the Hickman catheters remains unclear. Adherent fibrin at the catheter tip may also be important. Several reports suggest treatment with low dose thrombolytic therapy and antibiotics may be more effective than the same antibiotics given alone for some patients with catheter related infection (Ascher *et al.*, 1993; Jones *et al.*, 1993). Further research on the significance of biofilms and fibrin as factors in catheter related infection is awaited.

Source of Organisms Causing Catheter Related Infection:
Infection of central venous catheters may occur with the migration of adherent organisms along the external catheter surface after infecting or colonising the skin catheter entry site. The subcutaneous tunnel and cuff of the Hickman catheter were designed to minimise this mode of infection. Alternatively, organisms may invade by migrating down the luminal surface, after first contaminating the catheter hub (Collignon & Munro, 1989). Careful protocols to prevent catheter hub contamination would be expected to reduce this risk (reviewed by Putterman, 1990). Catheter related infection may develop rarely from the infusion of contaminated fluids, sometimes as outbreaks due to a single contaminated source (Pegues *et al.*, 1993).

Patients in whom Hickman catheters are inserted are often debilitated, immune suppressed, and frequently experience prolonged neutropenia after chemotherapy, enhancing the risk of infection. In these patients, particularly
if mucosal barriers are injured by chemotherapy, there may be translocation to, and colonisation of, the catheter by gut bacteria, occurring presumably during periods of asymptomatic bacteraemia (Tancrede & Andremont 1985). A similar finding has been reported in children with short bowel syndrome and central venous catheters. In one study, 19 of 28 cases of catheter sepsis the offending organism was present within the faecal flora, supporting translocation as an important mechanism of catheter infection in this patient group (Kurkchubasche et al., 1992).

Pathogenic organisms may be introduced at the time of catheter insertion if a break down in aseptic technique occurs leading to early nosocomial infection.

**Diagnosis and Definition of Catheter Related Infection**

Catheter related infection can be divided into three categories based on the predominant site of infection. Exit site infection refers to catheter infections localised to the exit site. Subcutaneous tunnel infections involve that part of the catheter which is placed subcutaneously, before entering the circulation. Catheter associated bacteraemia or fungaemia implies infection involving the intravascular portion of the catheter or, alternatively, the intraluminal surface.

The reported incidence of catheter related infection has varied from 2.7% to 60% (Groeger et al., 1993). Variation between studies of the definitions of infection used make direct comparisons of infection rates impossible.

Press et al. (1984) have provided a set of definitions for Hickman catheter infections which have provided a basis for subsequent studies. Their definitions are given here.

**Hickman catheter exit site infection:** development of erythema, tenderness, induration, and/or purulence within 2 cm of the skin exit of the catheter.

**Hickman catheter tunnel infection:** development of erythema, tenderness and induration along the subcutaneous tract ("tunnel") of the Hickman catheter at a distance >2 cm from the skin exit site with or without signs of inflammation or purulence at the exit site. Insertion site infections (that is the site used to insert the catheter through the vein wall) involve the tunnel and are considered in this category.

**Hickman catheter septicaemic infection:** development of fever and bacteraemia or fungaemia in a patient with an uninflamed catheter tract in whom fever and bacteraemia resolve within 48 hours upon removal of the catheter.
Hickman catheter septic thrombophlebitis: development of septic venous occlusion in proximity to the Hickman catheter associated with bacteraemia and fever.

The definition for catheter related sepsis has been modified by Mirro et al to include information from the catheter tip culture and from blood cultures performed on samples drawn simultaneously from the catheter and from a venipuncture (Mirro et al., 1989). Catheter tip culture is performed usually by the semi-quantitative method of Maki (Maki et al., 1977). In this method, an intravascular segment of the removed catheter is rolled on a sheep blood agar plate. The culture is considered to be positive if 15 or more colonies are present. Several investigators have suggested a lower cut off number of colonies to be significant in indicating catheter colonisation and/or infection of Hickman catheters (reviewed by Collignon & Munro, 1989).

Cultures of the catheter tip may provide retrospective confirmation of a clinical diagnosis of catheter related sepsis. Semi-quantitative cultures of intravascular catheters have been included in the Centers for Disease Control definitions for nosocomial venous infection (Garner et al., 1988). Similar information may be obtained by direct staining and microscopic examination of a catheter segment (Cooper & Hopkins, 1985). The clinical utility of these retrospective methods, as assessed by the degree in which test results effect management decisions, is low (Widmer et al., 1992).

Simultaneous peripheral and catheter blood cultures have been useful in the diagnosis of catheter related sepsis with high specificity (89%) but low sensitivity (Andremont et al., 1988). Catheter drawn specimens for culture are also very suitable for the diagnosis of non catheter related infections (Wormser et al., 1990). The definitions of Mirro et al for sepsicaemia and catheter related septicaemia extend those of Press et al. (1984) and are summarised here.

Septicaemia: growth of the same organism from two separate blood cultures or isolation of an organism from a single blood culture accompanied by symptoms and signs of infection.

Definite catheter related septicaemia: (1) fever and bacteraemia (or fungaemia) in the absence of an exit site or tunnel infection that resolved within 48 hours of catheter removal without alteration (or institution) of antimicrobial therapy; (2) organisms isolated in blood obtained from the catheter, but not in blood simultaneously obtained from venipuncture; or (3)
the same organism isolated from the blood and the catheter tip when the catheter was removed.

Quantitative blood culture techniques have been developed which allow the number of organisms per millilitre to be directly estimated (Yagupsky & Nolte, 1990). Such diagnostic methods, although labour intensive, have some putative advantages over the conventional, broth media based method. For example, in *Staphylococcus aureus* bacteraemia from any cause, high bacterial colony counts are associated with a poor prognosis (Whimbey *et al.*, 1987; Dugdale & Ramsey, 1990). In the diagnosis of catheter related sepsis, the comparison of quantitative blood cultures obtained from peripheral veins and Hickman catheters has been studied (Fan *et al.*, 1989). A central catheter to peripheral bacterial colony count ratio of greater than 7 correlated with a subsequent positive catheter tip culture. The sensitivity and specificity of quantitative paired central-peripheral blood cultures in the diagnosis of catheter related septicaemia remain to be defined (Yagupsky & Nolte, 1990). Recently it has been suggested that a central catheter to peripheral bacterial colony count ratio of greater than 4 should be used (Capdevila *et al.*, 1992).

Benezra *et al* (1988) have incorporated quantitative paired blood cultures into a definition of catheter related septicaemia. In their study of 488 Hickman catheters, exit site infection and catheter tunnel infection were defined as previously described by Press *et al* (1984).

**Catheter related septicaemia** was defined as present when:

1. positive blood cultures collected through the central venous (Hickman) catheter showed a 10-fold or greater colony count compared with peripheral quantitative blood cultures or
2. if peripheral cultures were not collected, a colony count of 100 colony forming units per ml or more in blood from the central catheter.

In addition, if any other clinically or microbiologically apparent source of bacteraemia was present then the diagnosis of catheter related septicaemia was not made.

New methods such as the acridine-orange leucocyte cytospin test and the nitroblue terazolium test have been described which may detect catheter related sepsis earlier than culture methods (Rushforth *et al.*, 1993). The sensitivity of the acridine-orange leucocyte cytospin test may allow for a reduction in the number of Hickman catheters removed on suspicion of
infection alone. This test has yet to be applied widely in studies of Hickman catheter related infection.

Microbiology of Hickman Catheter Related Infection

A diverse range of organisms have been associated with Hickman catheter related infection. Bacteria found in skin flora, particularly coagulase negative staphylococci and aerobic diptheriods, have become increasingly important as pathogens in patients with Hickman catheters in situ. These organisms, along with *Staphylococcus aureus*, have replaced aerobic gram negative rods as the major pathogens in catheter related infection. Table 2 lists organisms responsible for catheter infection from 13 combined studies reviewed by Clarke and Raffin (1990).

*Staphylococcus epidermidis* has been shown to migrate rapidly along the external surface of a tunnelled central venous catheter in an experimental model (Cooper et al., 1988). It is the most common organism causing catheter related infection in many studies (Clarke & Raffin 1990 and Table 2). *Staphylococcus epidermidis* has been associated with catheter related, right sided, endocarditis in severely immune suppressed bone marrow transplant recipients (Martino et al., 1990). In older studies, isolates of *Staphylococcus epidermidis* may have been erroneously discounted as contaminants.

Infection with *Staphylococcus aureus* has been accompanied by especially grave sequelae, including septic thrombosis, acute endocarditis and metastatic infection (George & Cornel, 1992; Raad et al., 1992). In one study of Hickman catheter infection due to this organism, 3 of 36 patients died due to progressive sepsis despite intensive treatment (Dugdale & Ramsey, 1990). Moreover, only 18% of these infections were cured without removal of the catheter. Infection involving the catheter tunnel, in particular, required catheter removal.

*Pseudomonas* species are also an important cause of catheter related infection in patients who are neutropenic or who suffer from AIDS. The majority of infections can be controlled with antibiotic therapy alone, avoiding catheter removal. Catheter tunnel infection with *Pseudomonas aeruginosa* has usually required catheter removal (Benezra et al., 1988). In a retrospective study of 584 patients with AIDS presenting over a 5 year period, 19 bacteraemic infections with *Pseudomonas* species were observed, of which 11 were Hickman catheter related (Nelson et al., 1991). In this study,
*Pseudomonas aeruginosa* was second only to *Staphylococcus aureus* as a cause of catheter related infection. Even in children with underlying HIV infection, the majority of catheter related *Pseudomonas* species infections can be controlled without catheter removal (Roilides *et al.*, 1992).

Catheter associated fungaemia is a particularly dangerous adverse event. In a retrospective study by Lecciones *et al.* (1992) of 155 episodes of catheter related fungaemia and cancer, the mortality rate among infected patients was 52%. Almost all infections were due to *Candida* species, predominantly *Candida albicans*. The high mortality rate was observed despite aggressive therapy with amphotericin B and catheter removal in most patients. Neutropenia, usually chemotherapy related, and multiple antibiotic use were frequent precursors of *Candida* infection. In a similar study in paediatric cancer patients the mortality rate was 19% (Dato & Dajani, 1990). Attempts to retain the catheter were associated with a poor outcome.
**Table II**

Spectrum of Organisms Responsible for Central Venous Catheter Infections (from a review of 13 studies by Clarke & Raffin, 1990)

<table>
<thead>
<tr>
<th>Organism Responsible</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>31</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>14</td>
</tr>
<tr>
<td>Group D streptococcus</td>
<td>3</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>6</td>
</tr>
<tr>
<td><em>Corynebacterium</em> species</td>
<td>11</td>
</tr>
<tr>
<td><em>Bacillus</em> species</td>
<td>3</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>7</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td>4</td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td>4</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>6</td>
</tr>
<tr>
<td>Other Gram-negative</td>
<td>3</td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>7</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>112*</td>
</tr>
</tbody>
</table>

* Total is greater than 100% because of mixed infections with some authors reporting multiple organisms.
Putative Risk Factors for Infection

A number of potential risk factors for infection complicating Hickman catheter use have been identified in previous studies (including randomised controlled trials). The most frequently observed risk factors are summarised here.

Nature of Underlying Illness:
Many people requiring Hickman or similar semi-permanent intravenous catheters suffer from chronic illnesses which are associated with impaired immunity. Immunocompromised patients which have been observed to have a particularly high risk of catheter related infection include patients suffering from AIDS (Raviglione et al., 1989; Mukau et al., 1992), prolonged severe neutropenia (Harvey et al., 1986), acute leukaemia and bone marrow transplantation (Groeger et al., 1993; Ranson et al., 1990).

Catheter Exit Site Dressing:
The type of dressing used over the catheter exit site may influence the risk of infection. Transparent semipermeable dressings have been widely used. They form an occlusive dressing and allow the exit site to be observed. A meta-analysis of 15 randomised trials comparing transparent dressings to conventional gauze dressings for the exit site of non-tunnelled central venous catheters has been reported (Hoffman et al., 1992). Transparent dressings were associated with an increased relative risk of infection (RR = 1.69), and of bacteraemia (RR = 1.63) compared to gauze dressings. Similar studies have not been performed with Hickman catheters.

Duration of Placement:
As would be expected, a positive relationship has been observed between the overall risk of Hickman catheter infection and the duration of placement (Fuchs et al., 1984).

Catheter Use:
The use of Hickman catheters for total parenteral nutrition has been observed to elevated the risk of infection when compared to other uses (Mulloy et al., 1991)

Single Versus Double Lumen Hickman Catheters:
Double lumen Hickman catheters are often used in situations where several intravenous infusions may be required simultaneously. An elevated risk of catheter related infection has been observed in association with double
lumen catheters compared to single lumen catheters in retrospective non-randomised studies (Early et al., 1990; Henriques et al., 1993). In a randomised controlled trial of non-tunnelled central venous catheters used for total parenteral nutrition, triple lumen catheters were more frequently infected than single lumen catheters (Clark-Christoff et al., 1992). Similar randomised trials with Hickman catheters have not been performed.

Criteria for Hickman Catheter Removal for Infection

Many Hickman catheter infections can be controlled with antibiotic therapy without removal of the catheter and guidelines for catheter salvage have been suggested (reviewed by Wickham et al., 1992). In brief, most authors suggest removal if there is catheter related bacteraemia and no response after 48 hours treatment, or if there is evidence of hypotension due to sepsis, or evidence of septic emboli or endocarditis. Catheter removal is required for bacteraemia due to Bacillus species, Corynebacterium species and Candida species. Tunnel infections due to Staphylococcus aureus or Pseudomonas species also require the Hickman catheter to be removed. Hickman catheter related septicaemia can often be managed successfully, even in the presence of neutropenia, using parenteral antibiotics without catheter removal (Press et al., 1984; Newman et al., 1989; Benezra et al., 1988). The outcome may be improved, however, by early catheter removal when fungaemia or Staphylococcus aureus bacteraemia is present (Dato & Dajani, 1990; Lecciones et al., 1992; Dugdale & Ramsey, 1990). In a prospective study by Benezra et al. (1988) 33 of 54 patients with catheter related sepsis were cured with antibiotic therapy alone, while in the remaining 21 instances the catheter was removed. Other studies in patients with malignant disease have shown catheter retention rates after antibiotic therapy of between 60% and 90% (Mirro et al., 1989; Press et al., 1984). Similar success rates with Hickman catheter retention have been reported in patients with HIV infection and catheter related septicaemia (Raviglione et al., 1989).

Venous Thrombosis and Hickman Catheter Occlusion

Thrombosis of any of the central veins due to Hickman catheter placement can cause substantial morbidity and may be, rarely, life threatening. Thrombosis of the superior vena cava is accompanied by clinical signs of bilateral engorgement of neck veins, facial swelling, and the appearance of collateral vessels over the chest wall. The syndrome may lead to cerebral oedema, coma and death. Thrombosis of the brachiocephalic vein is
accompanied by ipsilateral swelling of the neck and arm. Thrombosis of the subclavian or axillary veins produces venous engorgement in the affected limb.

Venous thrombosis is most often detected when upper limb venograms and or catheter contrast studies are performed for symptoms of thrombosis or for catheter blockage. In studies where venograms have been routinely performed in asymptomatic patients, very high rates of unsuspected thrombosis (often incomplete) have been found. In such a study by Haire et al. in adults treated with autologous bone marrow transplantation, 22 of 35, or 64%, of venograms showed evidence of thrombosis, with complete blockage of the subclavian vein in 10 (Haire et al., 1991). Most patients were asymptomatic even when the subclavian vein was completely occluded. The diagnosis of thrombosis may also be achieved using two-dimensional echocardiography supplemented with colour flow Doppler sonography (Hammerli & Meyer, 1993).

Hickman catheter occlusion may be complete with total obstruction of the catheter. More commonly however, there is simply increased resistance to flow. It is sometimes possible to infuse fluids through the catheter but not to withdraw blood, a so-called "one-way catheter". Such catheter malfunction can afflict up to 25% of Hickman catheters (Lokich et al., 1985).

Bern et al. (1990) have conducted a randomised controlled trial of mini-dose warfarin to prevent venous thrombosis in adult patients with solid tumours and Hickman catheters. Again, routine upper limb venography was performed. The observation period was 90 days. In the warfarin treated group 4 of 42 (10%) catheters were complicated by venous thrombosis versus 15 of 40 (38%) catheters in the control group.

Major venous thrombosis, detected clinically or at post-mortem examination was found to complicate Hickman catheter placement in 17% of patients with solid tumour malignant disease (Anderson et al., 1989). Thrombosis may be accompanied by bacteraemia, which is often resistant to therapy until the thrombotic lesion resolves (Rupar et al., 1990).

Blood clots can be frequently aspirated from asymptomatic, normally functioning Hickman catheters (Anderson et al., 1987). Many of these blood clots presumably embolise to the lungs without complication each time the catheter is flushed.
Hickman catheter related central vein thrombosis has been reported to cause clinical pulmonary embolus (Leiby et al., 1989: Hughes et al., 1989). Pulmonary embolus in this setting may be fatal (Anderson et al., 1989).

Thus, venous thrombosis is a very common accompaniment of Hickman catheter placement. It is often asymptomatic. The significance, clinically, of asymptomatic thrombosis is unclear. Catheter occlusion can occur due to deposition of fibrin and blood clot within the catheter lumen itself. Frequently, a fibrin sheath will develop over the catheter tip without any associated venous thrombosis. Data from a single trial suggest catheter related thrombosis can be largely prevented by mini-dose warfarin prophylaxis.

Pathogenesis of Hickman Catheter Related Thrombosis

Hickman catheters are constructed from a soft silicone elastomer. Catheters constructed from this material have been shown to have a lower risk of inducing thrombosis than polyethylene catheters (Pottecher et al., 1984). A small randomised trial comparing Hickman or Broviac catheters to polyvinyl chloride catheters found a thrombosis rate of 5% in both patient groups (Wagman et al., 1984). Thus, although an improvement upon older catheter designs, Hickman catheters remain thrombogenic. Platelet aggregation and initiation of the coagulation cascade may triggered by the catheter itself, or by associated endothelial damage. Infusion of some fluids including hypertonic parenteral nutrition solutions may initiate thrombosis (Brennan, 1985).

Fibrin Sheath:
The formation of a fibrin sheath enveloping the distal intravascular segment is a frequent cause of catheter blockage. In one radiological study of malfunctioning Hickman catheters, an occluding fibrin sheath was present in 57% of cases (Cassidy et al., 1987). Rarely, the enveloping fibrin sheath can be so extensive as to cause retrograde flow of infusate within the fibrin sheath to the catheter entry site with extravasation (Gemlo et al., 1988). The development of fibrin sheath can be detected early by measuring the resistance to flow within the catheter directly (Stokes et al., 1989). Catheter management protocols have generally included frequent bolus flushes of low dose heparin in order to prevent the development of intraluminal clots and fibrin sheaths (Fry, 1992). Despite these protocols, intraluminal blood clots are common, although the consequences of these in terms of rates of catheter blockage remain uncertain (Anderson et al., 1987)
The relationship of malignancy to an increased risk of thromboembolic diseases was described initially by Trousseau in 1865 and has subsequently been confirmed in many studies (Bunn & Minna, 1985). Carcinomas, particularly mucin producing adenocarcinomas, have the highest risk. Chemotherapy may contribute to a transient hypercoagulable state in patients with solid tumours, contributing to thrombosis risk (Levine et al., 1988).

Putative Risk Factors for Thrombosis and Catheter Malfunction

The determinants of central venous thrombosis related to Hickman catheters have been less carefully studied than the determinants of infectious complications. Risk factors that have been observed are discussed here.

Nature of Underlying Illness:
In a study of Hickman catheters in patients with solid tumours, a diagnosis of adenocarcinoma of the lung was associated with the highest risk of catheter related thrombosis (Anderson et al., 1989). Thrombosis rates, reported from cohort studies where the majority of patients suffered from haematological disorders, are lower than those reported where the majority suffered from solid tumours. Such indirect comparisons suggest a higher risk of major thrombosis in patients with solid tumours (reviewed by Leiby et al., 1989). Further studies are required to test this hypothesis. Distortion of the superior vena cava due previous thrombotic episodes or due to large mediastinal tumours can elevate the risk of thrombosis.

Catheter Use:
Continuous infusions of chemotherapeutic drugs such as 5-flourouracil may lead to thrombosis more frequently than bolus injections through the catheter (Lokich et al., 1985). Use of the catheter for total parenteral nutrition may be accompanied by an elevated risk of thrombosis although direct evidence is lacking (Mughal 1989).

Position of the Catheter Tip and Site of Insertion:
In a large retrospective study of implanted ports in patients with cancer, Puel et al found a strong relationship between catheter tip malposition and superior vena cava thrombosis (Puel et al., 1993). In this study of 379 ports, catheters inserted from the left side, with the catheter tip placed in the upper half of the superior vena cava or in the brachiocephalic vein had a 28.6% risk of inducing thrombosis compared to 1% for all other catheters. In a smaller
study of both Hickman catheters and ports, catheter tip position high within the superior vena cava or within the brachiocephalic veins led to thrombosis (Stanislav et al., 1987).

Migration of the catheter tip to an unsatisfactory intravascular or extravascular position is discussed in the next section. Incomplete occlusion, with failure of blood to be aspirated may occasionally be due to abutment of the catheter tip against the wall of the central vein, usually the superior vena cava (Cassidy et al., 1987). Improvement in catheter function can sometimes be obtained in these circumstances by changing the posture of the patient during catheter use.

Catheter Compression:
With percutaneously inserted Hickman catheters, compression of the catheter can occur as it passes between the clavicle and first rib prior to entering the subclavian vein (Aitken & Minton, 1984). Such compression can lead to postural catheter occlusion and, more importantly, catheter fracture, as discussed below.

Catheter Salvage After Central Vein Thrombosis
The traditional management of central venous thrombosis has included systemic anticoagulation and catheter removal (Lokich et al., 1985). Several investigators have demonstrated favourable outcomes with anticoagulation only, while maintaining the catheter in situ (Anderson et al., 1989). The local infusion of low dose urokinase has also been suggested to assist catheter salvage and to reduce morbidity from central vein thrombosis (Fraschini et al., 1987).

Hickman catheter occlusion, not associated with major venous thrombosis or catheter malposition, has been successfully relieved with low dose urokinase bolus injections (Anderson et al., 1987). This manoeuvre may fail in up to 68% of cases (Monturo et al., 1990). In these resistant cases, low dose infusions of urokinase, streptokinase or tissue plasminogen activator have been successful (Haire et al., 1990; Wickham et al., 1992). Although re-occlusion may occur, many Hickman catheters can be safely salvaged with these methods (Haire & Lieberman, 1992).
Catheter Migration And Dislodgement

Despite accurate placement of a Hickman catheter, it is possible for the catheter tip to migrate to an unsatisfactory position, such as the internal jugular vein (Rasuli et al., 1992). Migration may be triggered by paroxysmal coughing, and has been reported as a complication of cystic fibrosis (Jacobs & Zaroukian, 1991). Such catheters often function poorly and are more likely to cause venous thrombosis (Cassidy et al., 1987). More serious sequelae have been reported following erosion of a vein wall by the catheter tip with migration to an extravascular site. Subsequent infusions through the catheter can lead to catastrophic extravasation of infusate (Krasna & Krause, 1991; Cathcart-Rake & Mowery, 1991). Lateral orientation of the catheter tip, abutting the vein wall, may be a precursor to extravascular migration (Manheimer et al., 1992).

Catheter dislodgement due to accidental traction on the external portion of the catheter has caused significant catheter loss, both in adult and paediatric populations (Carde et al., 1989). The subcutaneous Dacron cuff is not firmly adherent to the subcutaneous tissues for several weeks and early dislodgement can therefore occur. Even minor degrees of dislodgement might be expected to cause migration of the Hickman catheter tip to a higher and possibly less satisfactory position within the superior vena cava or subclavian veins (Cassidy et al., 1987).

Management of Catheter Migration

Migratory catheter tips can sometimes be repositioned with guide wire manipulation (Rasuli et al., 1992). Minor dislodgement may leave the catheter in a usable position, however most dislodgements or catheter tip migrations lead to catheter loss.

Mechanical Failure or Fracture

As Hickman catheters may be in use for many months, they are subject to wear and tear, and particularly to accidental puncture. Repair of damaged Hickman catheters with silicone adhesive and replacement hub kits is possible. Rarely Hickman catheters have fractured at the site of compression between the first rib and the clavicle, leading to embolisation of the intravascular portion of the catheter into the pulmonary artery (Aitken & Minton, 1984). Compression of the catheter can be detected on plain
radiographs as the "pinch-off sign". A scoring system has been suggested (Hinke et al., 1990). Removal after a maximum of 6 months use has been recommended for "pinched-off" Hickman catheters (Lafreniere 1991).

**Acute Complications of Hickman Catheter Insertion**

The insertion procedure may be accompanied by bleeding often in association with accidental arterial puncture or traumatic pneumothorax. Although accidental arterial puncture has been reported as frequently as 6% of placements (Wisborg et al., 1990), significant bleeding is rare, even in populations with a high prevalence of coagulation disorders (Harvey et al., 1986). Pneumothorax is also uncommon, complicating 1-5% of percutaneously inserted Hickman catheters (Hughes et al., 1989; Wisborg et al., 1990). Pneumothorax of sufficient severity to require intercostal tube drainage remains infrequent. Higher rates of detection of unsuspected iatrogenic pneumothorax can be obtained if delayed chest radiographs are taken (Spiliotis et al., 1992).

Venous air embolism has been reported during use or removal of central venous catheters as has a single instance of intra cerebral air embolism during insertion of a Hickman catheter (Mennim et al., 1992; Dukes et al., 1991).
6. METHODS

Design

A retrospective records based cohort study of consecutive Hickman catheters placed in a population of patients with malignant or haematological disease attending the medical oncology and clinical haematology units within a large hospital was conducted. The unit of study was each individual Hickman catheter successfully inserted during the study period.

Ethical Considerations

The written permission of the ACT Health Ethics Committee was obtained to conduct the study. Clinical records and information used during the study was stored securely within a medical records storage room within Woden Valley Hospital. A computer data file, with patient identifying information removed, was used within the Australian National University (in a secure facility) to perform part of the data analysis.

Case Ascertainment

All Hickman catheters placed during a 36 month study period, from January 1989 to December 1991 inclusive, were identified by reviewing the clinical departments' records. Cross-checking of these records was performed by reviewing log books held in the angiography suites of the Radiology Department. Following the 36 month study period, study catheters remaining in situ were followed for a further 8 months. Data collection was performed in September 1992 and events included if they occurred prior to August 31, 1992.

Catheter Eligibility

Hickman catheters were included in the study if they were placed in patients cared for in the Clinical Haematology & Medical Oncology Department and inserted percutaneously by the Radiology Department. All eligible catheters were placed via a subclavian approach and featured a subcutaneous tunnel. Fully implanted ports were not included in the study, nor were other catheter types such as Groshong catheters.
Technique of Catheter Insertion

All catheters were inserted percutaneously using local anaesthesia and fluoroscopic control in the Radiology Department (see Section 4 for discussion). Placement procedures were performed by one of two consultant radiologists or by senior radiology registrars trained in the technique. Single lumen Hickman catheters were used unless a double lumen catheter was requested by the clinical team. Such requests were based on the expectation of a requirement for more than one intravenous infusion concurrently. The site of insertion (left or right) was chosen by the radiologist performing the placement. The inserting radiologists generally preferred the right sided approach although left sided catheters were freely inserted if preferred by the patient. The right sided approach was considered relatively contraindicated if previous surgery had occurred within the right shoulder region or if a right subclavian vein catheter had been used in the past. In these circumstances the left sided approach was used.

The insertion method has been described (Cockburn et al., 1992; Page et al., 1990; Robertson et al., 1989). The procedure was performed with the patient supine. Under aseptic conditions, a stab incision was made at the entry site below the junction of the lateral and middle thirds of the clavicle. The subclavian vein was punctured with a Chub needle and J-wire inserted, over which a peel-away sheath was introduced. The subcutaneous track was created with a tunnelling instrument (Heyd & Rosser, 1991). The catheter length was determined by laying it along the line on of the j-wire using fluoroscopy, with the aim of leaving the catheter tip at the right atrial-superior vena cava junction. The catheter was then filled with saline containing heparin and inserted through the peel away sheath and positioned with fluoroscopic control. Catheter function was assessed immediately after the procedure. The catheter exit site was covered with a semi-permeable transparent dressing (OpsiteR). An erect posterioanterior chest radiograph was taken after insertion to check the final position of the catheter tip and to exclude the immediate complications of pneumothorax and haemothorax.

Catheter Use and Care

There were no specific restrictions on clinical use of the catheters during the study period. Hickman catheters were used to infuse intravenous drugs and fluids including cytotoxic chemotherapy, blood products, and parenteral nutrition as required. Blood samples for testing were routinely drawn from
the catheter. All use of the catheter for treatment or blood sampling was performed by Registered Nurses trained in the technique. Following use, the catheter was flushed with 5 mls. of normal saline containing 50 units of heparin, and "locked" with the same solution.

When not in regular use, Hickman catheters were flushed at least weekly. The catheter exit site was dressed with a transparent semi-permeable dressing weekly. Although all use of the catheter for treatment or blood sampling was performed by professional nurses, some catheter care, including exit site dressings and catheter flushes, was performed by the patient or by a family member. Patients and family members performing such catheter care were trained by hospital nursing staff, and generally supervised by trained Community Nurses.

**Management of Hickman Catheter Complications**

Formal protocols for the management of catheter complications were not in place within Woden Valley Hospital during the study period. Catheter related infections were managed with antibiotics. Catheter removal was ordered by the responsible clinician if the infection seemed severe and unlikely to respond to antibiotic treatment. Other complications were likewise treated as determined by the clinician in charge. Specimens for microbiological testing were taken only if there was clinical evidence of infection. Blood for culture was obtained from the catheter and concurrently from a peripheral venipuncture in circumstances where catheter related septicemia was suspected. Swabs of the catheter exit site were taken for culture to investigate signs of exit site infection and also to investigate febrile illnesses. Quantitative blood cultures were not performed during the study period. The Hospital policy required all Hickman catheters removed for any reason to be referred for semi-quantitative tip culture. Semi-quantitative catheter tip cultures were performed according to the method of Maki et al. (1977).

**Data Collection**

Information was extracted retrospectively from each patient's medical record. All records were examined independently by me and one of two collaborators. In instances where a difference of interpretation of the clinical record occurred, the record was further reviewed conjointly by both of the investigators concerned and a consensus reached. Individual data forms were completed for each catheter. For each catheter, data were collected
relating to the patient’s age, gender, height, weight, diagnosis, and treatment. Details of the catheter placement procedure, and of catheter use and complications were also collected. The operator inserting the catheter (one of two interventional radiologists or an advanced trainee in radiology) was recorded. The patient was considered to be an inpatient if admitted to a hospital for at least 24 hours prior to catheter insertion.

**Radiological Review**

All post-placement radiographs were reviewed by one collaborating radiologist. All radiological reviews were performed without knowledge of the catheter outcome.

An assessment of the degree of compression of each catheter, as it passed between the first rib and the clavicle, was made according to the methods of Hinke et al. (1990). A catheter was graded as grade 0 if it ran a smooth curved course in the region of the clavicle and first rib with no narrowing. Grade 1 catheters showed a degree of bending or deviation from a smooth curved course but no luminal narrowing. Grade 2 catheters showed luminal narrowing as the catheter passed beneath the clavicle. Grade 3 has been defined as complete catheter fracture.

The position of the catheter tip was directly measured on the chest radiograph using the carina as the reference point. The distance of the catheter tip inferior to the carina was measured and recorded in centimetres. Thus a catheter which ended at the carina was recorded as zero cm. The tip position of catheters which ended superior to the carina within the upper superior vena cava were recorded as negative numbers. A satisfactory position was believed to be 2 cm or more inferior to the carina (see Figure 1). In the analysis, a catheter tip with a measured position of 2 cm or more was defined as lying within the right atrium or low superior vena cava, whereas a catheter tip with a position of less than 2 cm was defined as being in the high superior vena cava (Figure 2).
Figure 1
Chest radiograph showing a right sided Hickman catheter with catheter tip ending within the superior vena cava; the measurement of the catheter tip position relative to the inferior margin of the carina is demonstrated.
Figure 2
Chest radiograph showing a right sided Hickman catheter terminating in the high superior vena cava.
Case Definitions

The following definitions of outcomes were applied during data collection.

Obesity

The Quetelet body mass index (BMI) was calculated for each patient according to the formula: \( BMI = \frac{weight}{(height)^2} \) where the weight is given in kilograms and the height in meters. A patient was considered to be obese if the BMI was greater than or equal to 30 (Truswell, 1981).

Catheter Related Infection

The rationale for these definitions was discussed in Section 5. Exit site infection was defined as pain, tenderness, erythema or purulent exudate within 2 cm of the exit site. Tunnel infection was defined as pain, tenderness or erythema along the subcutaneous course of the catheter > 2 cm from the exit site. Septicaemia was defined as growth of an organism from 2 or more separate blood cultures or as growth from a single culture with signs and symptoms of sepsis. Catheter related septicaemia was defined as (1) septicaemia in the absence of an exit site or tunnel infection which resolved within 48 hours of removing the catheter without the addition of antibiotic therapy; (2) positive culture of blood drawn from the catheter but with a simultaneous negative blood culture obtained from venipuncture; (3) the same organism cultured from blood and from the catheter tip after catheter removal. Catheters with infection at multiple sites were scored as separately infected for each individual site.

Central Vein Thrombosis

The diagnosis of an episode of central vein thrombosis was based solely on the findings of upper limb venography. Thrombosis was said to be present if there was complete or near complete obstruction of the axillary or subclavian veins or of the superior vena cava by thrombus detected by venography. Venography was only performed in response to a clinical suspicion of thrombosis or catheter occlusion.

Hickman Catheter Occlusion

Catheter occlusion was defined as the inability to infuse fluids through the catheter or to aspirate blood from the catheter.
Catheter malfunction included all cases of catheter occlusion as well as catheters where fluids could be infused but through which blood could not be aspirated, that is, the so-called "one-way" catheters.

Hickman Catheter Migration or Dislodgement

Catheter migration was diagnosed when the catheter tip was found to have moved to an unsatisfactory position on radiographs or when the catheter either spontaneously or accidentally was completely or partially removed.

Hickman Catheter Failure

Catheter failure was defined as removal or loss of the Hickman catheter due to a complication in circumstances where there was a continuing need for intravenous access. Acceptable evidence of a continuing requirement for intravenous access was the placement a further semi-permanent device, or the use of peripheral intravenous cannulas for infusions, within 28 days of catheter removal.

Acute Complications of Catheter Placement

Pneumothorax and haemothorax were recorded when reported on the post insertion chest radiograph. Bleeding and haematoma after catheter placement was recorded if described in the medical record.
7. STATISTICAL METHODS

Data relating to each catheter were stored in a database using a personal computer. After the data were checked an initial descriptive analysis was performed. Statistics describing patient and catheter characteristics and the frequency of adverse events were calculated using the Epi Info version 5.1 computer program (Dean et al., 1990). The median duration of catheter placement was calculated as was the frequency of catheter infection per one hundred catheter days.

Analysis of time to catheter failure, and time to the development of catheter malfunction were performed using the product limit method of Kaplan and Meyer (Lagakos, 1992). In this analysis, catheters electively removed, lost to follow-up, or in use at the time of final analysis, without an event of interest having occurred, were considered to be censored observations. Catheters remaining in situ at the time of patient death were similarly censored.

A univariate assessment of potential risk factors for catheter failure was conducted. In this analysis, only the initial catheter inserted for any one patient was considered. Prospectively determined factors to be assessed were patient gender, diagnostic group (leukaemia versus non-leukaemia), obesity, site of catheter insertion, catheter tip position, and the operator inserting the catheter. The relative risk of failure in each group in the cohort (as defined by the risk factor in question) was calculated and Taylor Series 95% confidence intervals (CI) provided. The null hypothesis of no relationship existing between the factor and catheter failure was tested using Fisher's Exact test (Zelterman & Louis, 1992). A probability of less than 0.05 was considered sufficient to reject the null hypothesis. Two tailed tests were used throughout. A similar analysis, using the same factors, was performed to assess the determinants of catheter malfunction.

A secondary analysis was performed to assess potential risk factors for catheter related infection. Factors examined were gender, diagnostic group (leukaemia versus non-leukaemia), obesity, the number of catheter lumens (one versus two), and the operator inserting the catheter. Finally an analysis of risk factors for catheter migration or dislodgement was performed. Factors examined were patient obesity, site of insertion and the operator performing the insertion. Again, 95% confidence intervals for the relative risk were constructed and proportions compared with Fisher's Exact test. As the
number of comparisons was limited and the analysis prospectively defined a
correction for multiple comparisons was not applied.

Separate time to failure curves for groups within the cohort were constructed
using gender, catheter site, operator and obesity. These curves were
compared using the logrank test (Lagakos, 1992). A probability of less 0.05
was considered sufficient to reject the null hypothesis using a two-tailed test.
Time to malfunction curves were similarly constructed and tested using
catheter site and catheter tip position as factors.
8. STATISTICAL METHODS - MULTIVARIATE

The time to Hickman catheter failure was modelled in a multiplicative Cox proportional hazards model (Cox & Oakes, 1984). In order to ensure that each catheter analysed was fully independent, the analysis was performed only on the initial catheter placed in any one patient. Second or subsequent catheters, in a single patient, were thus excluded. The factors examined in the initial analysis, with the exception of obesity and catheter tip position, were added to the model in a stepwise procedure and their influence assessed by calculating the reduction of deviance (or the likelihood ratio statistic). The body mass index and the catheter tip position in centimetres were modelled as continuous explanatory variables rather than as factors. Explanatory variables and factors were retained in the model if the reduction of deviance was greater than would be expected by chance. The null hypothesis of no reduction in deviance was rejected at a probability of less than 0.05.

Parameters were calculated using a personal computer and the EGRET computer program (Epidemiological Graphics, Estimation and Testing package, version 0.2.6; Serc & Cytel, 1991). The adequacy of the fitted model was assessed by examining the delta-beta residuals graphically and found to be adequate. The assumption of proportional hazard was checked by examining the effect of adding an interaction term including log time for each significant explanatory variable, to the final model (EGRET Manual, revision 4, page 204).
9. RESULTS

Patient and Catheter Characteristics

Over the 3 year study period there were 153 Hickman catheters provided for 122 patients. There was also 1 Groshong catheter inserted and 24 ports implanted. Of the 153 Hickman catheters inserted, 1 catheter was excluded because of insertion via the femoral vein and 2 were excluded because the medical records were not available for review.

A total of 150 catheters placed in 120 patients therefore were available for inclusion in the study cohort.

The patient characteristics are summarised in Table III. The mean patient age was 49.5 years (range 14 to 78). At the time of final analysis, eight months after the end of the study entry period, 62 patients (56%) had died of their underlying disease and 48 (44%) were alive.

The details of catheter insertion and use for all study Hickman catheters are summarised in Table IV. The right subclavian approach was chosen for catheter placement for 69% of all catheters (73% of catheters where the site of insertion was recorded). When second or subsequent Hickman catheters inserted in the one patient are excluded, right sided catheters were more strongly preferred, representing 77% of catheters inserted (92 of 120). Of the 30 replacement catheters inserted during the study period 17 (57%) were left-sided. The reason for selecting the right or left site for insertion was not usually recorded in the clinical record.

Most Hickman catheters inserted were double lumen catheters, reflecting the anticipated complexity of the planned intravenous therapy.

Only 10% of the catheters were used for total parenteral nutrition (TPN). As might be expected in this patient population, the major use of the catheters was for some form of chemotherapy.

Although these catheters are easily inserted in the outpatient setting, the large majority (77%) of recipients were inpatients at the time of catheter insertion.
Table III
Patient Characteristics

N=120

Demography

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>64</td>
<td>53%</td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
<td>46%</td>
</tr>
<tr>
<td>Age</td>
<td>49.5 years</td>
<td>(mean)</td>
</tr>
</tbody>
</table>

Body Mass

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>18</td>
<td>15%</td>
</tr>
<tr>
<td>Non-obese</td>
<td>102</td>
<td>85%</td>
</tr>
</tbody>
</table>

Disease

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>22</td>
<td>18%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>27</td>
<td>23%</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>58</td>
<td>48%</td>
</tr>
<tr>
<td>Other*</td>
<td>13</td>
<td>11%</td>
</tr>
</tbody>
</table>

* Other = multiple myeloma 3, myelodysplasia/AML 6, HIV/Kaposi 1, vasculitis 1, DVT 1, aplastic anaemia 1.
Table IV
Characteristics of Hickman Catheter Insertion and Use

N=150

Site of Insertion

<table>
<thead>
<tr>
<th>Site</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>103</td>
<td>69%</td>
</tr>
<tr>
<td>Left</td>
<td>38</td>
<td>25%</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>6%</td>
</tr>
</tbody>
</table>

Number of Catheter Lumens

<table>
<thead>
<tr>
<th>Lumens</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lumen</td>
<td>32</td>
<td>21%</td>
</tr>
<tr>
<td>Double lumen</td>
<td>117</td>
<td>78%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

Parenteral Nutrition

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPN</td>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td>No TPN</td>
<td>135</td>
<td>90%</td>
</tr>
</tbody>
</table>

Use for Chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>110</td>
<td>73%</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>40</td>
<td>27%</td>
</tr>
</tbody>
</table>

Initial or Replacement Catheter

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First catheter</td>
<td>120</td>
<td>80%</td>
</tr>
<tr>
<td>Second</td>
<td>21</td>
<td>14%</td>
</tr>
<tr>
<td>Third or more</td>
<td>9</td>
<td>6%</td>
</tr>
</tbody>
</table>

Status at Time of Insertion

<table>
<thead>
<tr>
<th>Status</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>115</td>
<td>77%</td>
</tr>
<tr>
<td>Outpatient</td>
<td>35</td>
<td>23%</td>
</tr>
<tr>
<td>Number of catheters</td>
<td>Patients</td>
<td>Percentage</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>99</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>
Of 120 patients in the study, 99 had only one catheter inserted, while 21 had 2 to 5 catheters inserted during the study period (Table V). Second or subsequent catheters were more likely to be inserted via the left side (92/120 versus 17/30; Fisher's Exact p<0.001) and were more frequent in patients with leukaemia (16/38 versus 14/112; Fisher's Exact p=0.001). There were no differences in the number of catheter lumens or in the use to which the catheter was put between initial and replacement catheters (data not shown).

Outcome of Catheter Placement

Findings of Radiological Assessment

Post insertion chest radiographs were available for review for 140 catheters. The mean distance of the catheter tip as measured inferior to the carina was 2.39 cm (standard deviation 2.5, range 16 to 11 cm). The was no difference in the mean catheter tip position for the three operators inserting catheters.

Radiographs were interpretable regarding catheter compression for 138 catheters. There was no compression of 101 catheters (73%), grade 1 compression of 28 catheters (20%) and grade 2 compression of 9 catheters (7%). Grade 1 or 2 compression was more frequent with left sided catheters (16/38 versus 21/98; Fisher's Exact p=0.02). Despite the observed frequency of catheter compression, there were no reported instances of catheter fracture within the study cohort.

Acute Complications of Hickman Catheter Placement

Acute complications were rare and mild. There was a single occurrence of accidental arterial puncture which was not accompanied by significant bleeding or other sequelae. One episode of exit site bleeding was recorded in a patient with acute myeloid leukaemia and disseminated intravascular coagulation. One occurrence of tunnel haematoma was also encountered. Neither of these complications lead to significant morbidity or to catheter loss. Traumatic pneumothorax was not observed during the whole study period. Also, no case of previously unrecognised pneumothorax was observed during the radiological review of all available post insertion chest radiographs.

Outcome of Catheter Use

The median time until catheter removal for any reason was 55 days (range 1 to 650). The total duration of use for all catheters was 14,225 patient days.
Study catheters remained in situ at the time of the death of 42 patients (28% of all catheters). Five catheters (3%) were lost to follow up due to patient transfer to another institution after a median observation period of 27 days post insertion (range 14 to 148). A total of 103 catheters were actually removed within Woden Valley Hospital. Complications led to the non-elective removal (or catheter failure, as defined) of 48 catheters (32% of all catheters). The remaining 55 catheters (37%) were removed electively when intravenous access was no longer required. Thus 68% of catheters remained functional until regular intravenous access was no longer required, the patient was lost to follow up, or died with the catheter in situ. There were no patient deaths recorded related to any catheter complication.

**Catheter Failure**

Hickman catheter failure occurred on 48 occasions or 32% of all catheters. The causes of catheter failure were as follows: infection or suspected infection in 22 catheters (46% of failures), blockage or malfunction with or without venous thrombosis in 18 catheters (37%), and catheter migration or dislodgement in 8 (17%). The features and determinants of these specific adverse events are discussed in later sections.

The determinants of overall catheter failure were examined. A univariate analysis of potential risk factors for catheter failure was performed. Male gender was associated with a relative risk of catheter failure of 2.02 compared to female gender (95% confidence interval 1.13 to 3.6, Fisher's Exact p=0.017). Left sided catheter insertion was associated with a relative risk of 2.3 compared to right sided insertion (95% confidence interval 1.12 to 3.55, Fisher's Exact p=0.057). The other potential risk factors examined, including obesity of the catheter recipient, were not associated with an increased risk.

The duration of catheter use without failure was examined using product limit survival curves. The time to failure for all 150 study catheters is shown in Figure 3. The actuarial median time to failure was 176 days. Survival curves were constructed for identified risk groups using only data from the 120 initial Hickman catheters inserted. The median time to failure for initial catheters in males was 162 days versus 308 days for females (logrank p=0.026, Figure 4). Curves for right and left sided catheters are shown in Figure 5. The median time to failure was 170 days for left sided catheters and was not reached for right sided catheters (logrank p=0.098).
Figure 3

Time to Hickman Catheter Failure
Figure 4

Time to Hickman Catheter Failure

Males versus Females

Note: Only the initial catheter inserted into any patient is included (N=120).
Figure 5

Time to Hickman Catheter Failure
Right versus Left Sided Insertion

Note: Only the initial catheter inserted into any patient is included (N=120).
Cox multiplicative proportional hazards models for time to catheter failure were constructed. A series of models including potential risk factors were examined in a stepwise procedure as described in the methods section. Significant predicting factors of the time to catheter failure included in the final model were:

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>HAZARD RATIO</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion site (R vs L)</td>
<td>2.2</td>
<td>1.03 &amp; 4.76 p=0.041</td>
</tr>
<tr>
<td>Gender (M vs F)</td>
<td>2.4</td>
<td>1.16 &amp; 4.92 p=0.019</td>
</tr>
<tr>
<td>BMI (body mass index)</td>
<td>1.1</td>
<td>1.03 &amp; 1.18 p=0.005</td>
</tr>
</tbody>
</table>

The hazard ratio for the BMI may be interpreted as the ratio of hazard of catheter failure experienced by each catheter per each unit increase in the index, controlling for the other factors in the model. The BMI was included in the model in units of kilograms per meter².

The patient diagnostic group, the operator inserting the catheter, the number of catheter lumens and the catheter tip position were not predictors of time to catheter failure in this model.

The Cox survival analysis confirmed the site of insertion and patient gender as predictors of reduced time to catheter failure. The model also showed BMI to be independently associated with early catheter failure, even though the univariate analysis failed to show an association between obesity and the overall failure rate. The mechanism of catheter failure associated with these risk factors is explored in following sections describing specific types of complication.

**Hickman Catheter Related Infections**

Catheter related infections were common, complicating 40 catheters (27%). Many of these infections were mild. However 18 catheters were lost due to infection and a further 5 were removed when infection was suspected but subsequently not proven. Thus a total of 23 catheters (15%) failed due to infection or suspected infection during the study period. There were, overall, 0.28 catheter infections per 100 catheter days.

**Exit site infections**

Signs and symptoms of Hickman catheter exit site infection were recorded in relation to 33 catheters (22%). They were generally managed with antibiotics
and/or local toilet with frequent dressing changes. There were 8 catheter failures (5% of all catheters) due to exit site infections alone. Of the 33 infected catheter exit sites 26 occurred in 120 initial catheters, the remainder (7) occurring in replacement catheters.

Risk factors for exit site infection:
In an examination of the 120 initial catheters, male gender was associated an increase in exit site infections, with a relative risk, male versus female, of 2.6 (95% CI 1.2 to 5.4, Fisher's Exact p=0.014). When all 150 catheters were included in the analysis the relative risk, male versus female was 2.3 (95% CI 1.2 to 4.2, Fisher's Exact p=0.02). There was no relationship present between the other factors examined and the risk of exit site infection.

Microbiology of exit site infection:
Catheter exit site swabs were submitted for microbiological examination at least once for all 33 recorded exit site infections and also for 23 exit sites where infection had not been recorded. The latter exit site swabs were taken as part of the routine investigation of fever. The microbiological culture findings were not part of the definition of exit site infection applied in this study. Of 50 cultures taken from 33 exit sites with clinical signs of infection, 20 cultures (from 13 catheter exit sites) were reported as showing coagulase negative staphylococci only. These organisms were also present in 14 of 33 cultures from 23 non-infected catheter exit sites. As coagulase negative staphylococci are normal skin commensal bacteria, the significance of the detection of these organisms in this site (as distinct from blood or catheter tip cultures) is uncertain. Four clinically infected sites were culture negative including 1 catheter which was removed for exit site infection. The culture results from infected sites are summarised in Table VI and from non-infected sites in Table VII. No clearly pathogenic organisms were obtained from non-infected sites, and the utility of this routine investigation in febrile patients is uncertain.
Table VI

Microbiological Isolates From Hickman Catheter Exit Sites Where Infection Was Clinically Present

<table>
<thead>
<tr>
<th>Organism</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase neg. staphylococci</td>
<td>13</td>
<td>39%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>11</td>
<td>33%</td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Group D streptococcus</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td><em>Corynebacteria</em></td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td><em>Serratia</em></td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>

* A total of 33 isolates were obtained from 33 clinically infected exit sites. Although 4 clinically infected exit sites did not yield any organisms, 4 clinically infected exit sites returned 2 organisms; a total of 50 examinations were performed on the 33 exit sites.
Table VII

Microbiological Culture Results From Hickman Catheter Exit Sites
Where Infection Was Clinically NOT Present

N=23

<p>| | | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>Coagulase neg. staphylococci</td>
<td>10</td>
<td>44%</td>
</tr>
<tr>
<td>Corynebacteria</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>No growth</td>
<td>12</td>
<td>52%</td>
</tr>
</tbody>
</table>

^ A total of 33 examinations were performed on 23 catheter exit sites.
Staphylococcus aureus was only recovered from clinically infected exit sites. This organism was the most important single cause of exit site infection. The exit site cultures from the 8 catheters removed because of isolated exit site infection returned Staphylococcus aureus from 3, Pseudomonas species from 2, and coagulase negative staphylococci from 2. As noted previously, 1 culture was negative.

Subcutaneous tunnel infections

Three subcutaneous tunnel infections were observed with an overall incidence of 2%. One infection was mild and culture negative. The 2 other infections were severe, in both instances requiring removal of the catheter 9 days after insertion. In one patient blood cultures grew Staphylococcus aureus and Candida albicans and in the other the catheter tip culture was positive for coagulase negative staphylococci.

Hickman catheter related septicaemia

Catheter related septicaemia, as defined, complicated 11 Hickman catheters (7%) in 8 patients and led to the removal of 7 catheters (5%). A further 5 catheters were removed for suspected catheter related sepsis with negative blood cultures. In 2 of these instances the catheter tip semi-quantitative culture was positive, suggesting a significant infection may have been present. The microbiological isolates from blood cultures taken from patients with catheter related sepsis are summarised in Table VIII.
Table VIII

Microbiological Isolates from Blood in Catheter Related Septicaemia

N=11

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase neg. staphylococi</td>
<td>5</td>
<td>45%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3</td>
<td>27%</td>
</tr>
<tr>
<td><em>Corynebacteria</em></td>
<td>1</td>
<td>9%</td>
</tr>
<tr>
<td><em>Serratia</em></td>
<td>1</td>
<td>9%</td>
</tr>
<tr>
<td><em>Micrococcus</em></td>
<td>1</td>
<td>9%</td>
</tr>
</tbody>
</table>
Exactly half of the patients who suffered from catheter related sepsis complicating their initial Hickman catheter had underlying acute leukaemia. The diagnosis of acute leukaemia was the only identified risk factor for catheter related sepsis (relative risk leukaemia versus non-leukaemia = 3.11, 95% CI 1.4 to 7.0, Fisher’s Exact p=0.036).

Catheter tip culture results:
Semi quantitative culture of the catheter tip was performed on 73 of 108 removed catheters including 20 of 22 catheters removed for proven or suspected catheter related infection. The microbiological isolates from these cultures are summarised in Table IX. Again both coagulase negative staphylococci and \textit{Staphylococcus aureus} were prominent pathogens in this setting. These two organisms were cultured from 65% of catheters removed for suspected or proven infection. They were also found infecting or at least colonising 25% of catheter tips sent for routine surveillance culture. Four catheter tips yielded cultures of \textit{Staphylococcus aureus} even though they were not removed because of infection. In 3 of these instances there was a documented exit site infection due to \textit{Staphylococcus aureus} present, which may have allowed contamination of the catheter tip to occur at the time of elective catheter removal.

Overall the data relating to catheter infection reveal a high incidence of significant infection due to gram positive organisms, generally coagulase negative and coagulase positive staphylococci.
Table IX
Microbiological Isolates from Hickman Catheter Tip

Catheters removed for suspected or proven infection

<table>
<thead>
<tr>
<th></th>
<th>N=20*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase neg. staphylococci</td>
<td>8</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>\textit{Staphylococcus aureus}</td>
<td>5</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>\textit{Corynebacteria}</td>
<td>1</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>\textit{Serratia}</td>
<td>1</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>no growth</td>
<td>5</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

Catheters removed for reasons other than infection

<table>
<thead>
<tr>
<th></th>
<th>N=53^</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase neg staphylococci</td>
<td>9</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>\textit{Staphylococcus aureus}</td>
<td>4</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>no growth</td>
<td>40</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

* A further 2 catheter tips were not submitted for examination.

^ A further 28 catheter tips were not submitted for examination.
Venous Thrombosis and Hickman Catheter Malfunction

Some form of catheter blockage, thrombosis or malfunction was observed to complicate 44 catheters (29% of all catheters).

Venous Thrombosis

Clinical signs of major thrombosis were observed in 4 patients; 2 developed the syndrome of superior vena cava obstruction and 2 developed ipsilateral arm swelling. Upper limb venography or catheter contrast radiographs were performed in response to catheter malfunction or signs of venous obstruction. An example of a contrast catheter radiograph demonstrating venous thrombosis is provided in Figure 6. Venous thrombosis, confirmed radiologically with these methods, was seen complicating 12 Hickman catheters (8%). No patient developed venous thrombosis on more than one occasion. Most cases of venous thrombosis were managed by catheter removal (10 of 12 affected catheters). Two catheters were salvaged with infusions of low dose streptokinase. Heparin anticoagulant therapy was instituted in 7 of 12 patients with thrombosis. All patients recovered from the episode of thrombosis without long term sequelae.

One patient with a subclavian vein thrombosis developed dyspnoea and hypoxaemia 2 days after venography and catheter removal. A ventilation/perfusion lung scan showed several perfusion defects without matching ventilation defects, strongly suspicious of pulmonary embolism. No other site of venous thrombosis was clinically apparent. The patient made a full recovery following treatment with systemic anticoagulant therapy.

Potential risk factors for venous thrombosis examined were insertion site, catheter tip position, patient gender, and diagnosis of the underlying disease. Only data relating to the initial catheter for each patient was included. For left sided catheters the risk of thrombosis was 19% compared to 5% for right sided catheters (relative risk left versus right 4.38, 95% CI 1.19 to 16; Fisher's Exact p=0.038). No increase in the risk of venous thrombosis was observed due to the other factors examined.
Figure 6
Hickman catheter venogram showing thrombus encasing the catheter tip within the superior vena cava.
Hickman Catheter Malfunction

Catheter malfunction was a frequently encountered phenomenon, affecting 44 catheters (29%). The malfunctions ranged from intermittent difficulty in aspirating blood through the catheter to complete blockage associated with major venous thrombosis. All 12 catheters complicated by venous thrombosis had some degree of malfunction. The majority of these catheters, 7 of the 12, were completely blocked. A total of 18 catheters (12%), including 10 of the 12 catheters associated with venous thrombosis, were lost due to these complications.

Of 44 catheters observed to malfunction, 10 became completely blocked while 34 were partially blocked, with difficulty or inability to aspirate blood. Nine of the blocked catheters were removed and replaced because of blockage and/or associated venous thrombosis. Thrombolytic therapy with low dose streptokinase was attempted with 3 of the blocked catheters, but resulted in catheter retention on only 1 occasion.

There were 34 (23%) partially blocked or "one-way" catheters. This form of malfunction was often intermittent. On investigation with contrast studies 5 of these partially blocked catheters were associated with venous thrombosis. Nine partially blocked catheters were eventually removed and replaced because of persisting poor function or associated venous thrombosis. Low dose streptokinase was administered successfully to clear a single catheter.

The relationship between Hickman catheter malfunction in the initial catheter inserted into each patient and potential risk factors was examined. No difference in the risk of malfunction was observed due to patient gender, the presence of obesity, patient diagnostic group or the operator inserting the catheter. Of the initial catheters where the site of insertion was recorded, 10 of 21 (48%) left sided catheters developed malfunction compared to 17 of 75 (23%) right sided catheters (relative risk of left versus right 2.58, 95% CI 1.38 to 4.8, Fisher's Exact p<0.01). Moreover 6 of 21 (29%) left sided catheters actually failed because of catheter blockage/malfunction compared to only 5 of 92 (5%) right sided catheters (relative risk of left versus right 5.26, 95% CI 1.8 to 16, Fisher's Exact p=0.005). The number of excess catheter failures due to blockage of left sided catheters is sufficient to account for the overall increase in catheter failure observed for left sided catheters.
The position of the catheter tip, as measured on post insertion erect radiographs, was defined as lying within the high superior vena cava if it was less than 2 cm inferior to the carina. Catheter malfunction occurred in 14 of 40 (35%) high position catheters compared to 14 of 73 (19%) low position catheters (relative risk high versus low catheter position 1.8, 95% CI 0.97 to 3.43, Fisher's Exact p=0.07).

Some form of malfunction was more frequently encountered with double lumen catheters compared to single lumen catheters. When the initial catheter inserted in each patient only is considered there were 2 of 25 (8%) cases of malfunction for single lumen catheters versus 29 of 95 (31%) double lumen catheters (relative risk double lumen versus single lumen of 3.81, 95% CI 1.0 to 15, Fisher's Exact p=0.02). There was no difference in the risk of venous thrombosis comparing single to double lumen catheters nor in the risk of complete catheter blockage. The excess catheter malfunction observed with double lumen catheter was due to partial catheter blockage, that is, the inability to aspirate blood. Of 25 single lumen catheters there were no instances of reported isolated partial catheter obstruction, although there were 2 single lumen catheters which became completely obstructed. This experience compares with 24 of 95 (25%) double lumen catheters in which isolated partial blockage developed (Fisher's Exact p<0.01). The marked increase risk of catheter malfunction due to partial blockage in double lumen catheters did not lead to any increase in frequency of catheter failure and replacement. Partial catheter blockage or failure to aspirate was assigned when either lumen of a double lumen catheter was observed to be malfunctioning as recorded in the medical record. The presence of two lumens in a catheter might be expected to increase the risk of an lumen specific event simply because there is twice the number of lumens to malfunction, relative to the single lumen catheter. Specific information about the functional state of each catheter lumen was not available. However, even when the frequency of partial catheter obstruction is calculated per lumen (rather than per catheter), there remains an excess risk with double lumen catheters (15% versus 0, Fisher's Exact p=0.048). This method may underestimate the risk per lumen in double lumen catheters, as it assumes that no catheter was observed to develop partial obstruction of both lumens simultaneously.

A Cox proportional hazards survival analysis was performed with the time to first occasion of catheter malfunction of any kind as the endpoint of interest.
A series of models including potential risk factors were examined in a stepwise procedure as described in the methods section.

Patient age, gender and type of underlying disease were not significant predictors of time to malfunction and were excluded from the model. The catheter tip position and the operator inserting the catheter were likewise omitted. Predictors of reduced time to catheter malfunction included in the final model were:

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>HAZARD RATIO</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion site (R vs L)</td>
<td>3.5</td>
<td>1.5 to 8.3</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>1.1</td>
<td>1.0 to 1.2</td>
<td>0.041</td>
</tr>
<tr>
<td>Lumens (1 vs 2)</td>
<td>6.9</td>
<td>0.92 to 52</td>
<td>0.06</td>
</tr>
</tbody>
</table>

The hazard ratio for the BMI may be interpreted as the ratio of hazard of malfunction experienced by each catheter per unit increase of the BMI. The BMI was included in the model in units of kilograms per meter$^2$.

The Cox survival analysis confirmed the insertion site and the number of catheter lumens as important predictors of catheter malfunction. Additionally, the BMI was identified as a predictor of malfunction, even though obesity (that is, a BMI greater than 30) was not associated with malfunction in the univariate analysis. In this analysis, the catheter tip position was no longer a predictor of time to malfunction when the site of insertion, the BMI, and the number of lumens were controlled.

**Hickman Catheter Migration or Dislodgement**

Migration of the catheter tip to an unsatisfactory position, and or accidental dislodgement of the catheter was observed to complicate 11 catheters (7%). On 2 occasions dislodgement was due to the accidental complete removal of their Hickman catheter by confused patients. On 2 other occasions the catheter tip migrated spontaneously to the neck, from an initially satisfactory position within the superior vena cava. Both these catheters were able to be salvaged with the catheter tip being manipulated with a guide wire into an acceptable position. One catheter became dislodged, with the subcutaneous cuff fully extruded from the exit site. This partially retained catheter was able to secured in place with dressings and to be used until intravenous access was no longer required. Eight of the 11 catheters observed to migrate or
become dislodged were eventually lost because of this complication (5% of all catheters).

Patient obesity (as defined) was associated with an increased risk of catheter migration/dislodgement (relative risk obese versus non-obese 4.5, 95% CI 1.34 to 15, Fisher's Exact p=0.03). No other factor examined was associated with an increased risk of catheter migration/dislodgement.

Four of 18 initial Hickman catheters inserted into patients with a BMI greater than 30 were observed to suffer migration or dislodgement. All these catheters were removed because of this complication. Of the 5 catheters which migrated or were dislodged in non-obese patients, 3 were removed. For all 150 study catheters, 11 cases of catheter failure in obese patients were observed. Catheter migration or dislodgement was the major cause of failure in this patient group, accounting for the loss in 5 of the 11 failed catheters, compared to 3 due to infection and 3 due to blockage. Among the 126 catheters inserted in non-obese patients only 3 were removed because of migration or dislodgement. The excess risk of catheter failure observed in obese patients is thus predominantly due to the risk of migration or dislodgement experienced by this patient group.

There was no difference in the observed frequency of catheter migration of dislodgement between groups defined by patient diagnosis (leukaemia versus non-leukaemia), catheter insertion site (right versus left) or the operator inserting the catheter. The position of the catheter tip as measured on the post insertion chest radiograph also did not predict ultimate catheter migration.

**Type of Vascular Access Used After Hickman Catheter Failure**

Of the total cohort of 150 study catheters placed in 120 patients, there were 48 catheter failures. The definition of catheter failure implied the ongoing need for vascular access following catheter removal. The type of vascular access device employed after Hickman catheter failure was recorded for 45 catheters. A replacement Hickman catheter was inserted on 21 occasions (47%) for 16 patients. Standard peripheral cannulas were used on 22 occasions (49%) and fully implanted ports were placed on 2 occasions (4%).

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10. DISCUSSION

This study describes the experience of Hickman catheter use in one centre caring for a mixed population of patients within a combined haematology and medical oncology service. Catheter care and maintenance protocols were uniform across the patient population. The catheter insertion technique was also uniform. Although there were no formal protocols in place during the study period for the management of catheter related complications, the same physicians cared for patients in all diagnostic groups and presumably applied similar clinical decision making rules to each catheter. The study therefore offers an opportunity to gain insight into Hickman catheter use, adverse events, and the determinants of adverse events in a setting which should be applicable to a wide range of haematology or medical oncology hospital departments.

Impact of the Study Design

The retrospective study design required the use of existing clinical records. The study was thus able to be completed relatively quickly despite a cohort enrolment period spanning 3 years. A minimum follow up period of 8 months was also feasible because of the retrospective design.

A retrospective design is associated with a number of disadvantages when compared to prospective studies. The main source of information was the patient medical record. These were completed to varying degrees of quality. Information relating to adverse events was primarily derived from this source. Particularly in regard to infection and poor function, the description of the catheter related events provided in the clinical record was critical in determining these study outcomes. Information was recorded in these records by both medical and nursing staff.

Given that the clinical records were completed by hospital staff without consideration of their possible use in this study there are potential errors in determining catheter outcomes. Possible sources of bias will be discussed in relation to each individual study endpoint.

Some potentially important putative risk factors for Hickman catheter complications could not be studied because insufficient information was available. In particular, the patient functional status was not recorded for majority of catheter recipients at the time of catheter insertion. Although
post-insertion chest radiographs were performed after all catheter insertions, these were not available for review for 10 of 150 catheters. In these cases the radiographic films either missing within the Hospital or had been removed to other institutions.

The retrospective study design may have some advantages over prospective studies. As discussed by Ransom et al. (1989) the act of enrolling a patient into a prospective study may influence the attitude of professional staff to catheter care and act to minimise complications during the study period. Such an effect has been observed by Wagman et al. (1984) who reported a reduction in the incidence of catheter related infection when a randomised controlled trial was commenced. In this respect, a retrospective study has the advantage of obtaining information in an environment of standard catheter care. Thus the results of a retrospective study should be more readily generalised to standard "non-trial" practice.

**Hickman Catheter Failure**

Catheter failure was defined in such a way as to minimise the potential for misclassification. Thus catheter failure was recorded only if removal occurred because of any perceived or real complication and if there was subsequently clear evidence of a continuing requirement for vascular access. A Hickman catheter being maintained "just in case" clinical circumstances arose where it might be needed (for example, a patient who has just achieved a complete remission but in circumstances where early relapse is possible) would not be classified as a failure if its removal was triggered by a complication and a subsequent intravenous infusion was not required within 28 days. The determination of catheter failure is therefore robust within the study.

The Hickman catheter failure rate of 32% observed in this study falls within the upper range of failure rates reported from comparable studies (see table I, page 14). The median duration of catheter use of 55 days is similarly comparable.

Multiple insertions of Hickman catheters were frequent during the study period (see Table V, page 45). Not all of these insertions were required because of catheter failure, some catheters being removed electively and then replaced when a further indication for durable intravenous access arose.
The repeated need for catheter insertions due to catheter failure represents a significant burden for the patients involved as well as additional cost. Many complicated Hickman catheters can be salvaged with appropriate treatment. The overall failure rate is dependant not only on the frequency and severity of catheter complications, but also on the clinical management of these complications. Catheter removal is warranted if it shortens the duration of the catheter related illness or reduces the risk of important sequelae. As will be discussed, catheter removal may have been undertaken more frequently during this study than in some prospective studies because of the absence of explicit guidelines for the treatment of catheter infection and poor function or thrombosis.

**Hickman Catheter Related Infections**

The most frequently observed complication of Hickman catheter use in this study was infection. Catheter related infections were observed to complicate 27% of all catheters. The majority of infected catheters exhibited exit site infection (33 of 40 infected catheters).

There were 0.28 infections observed per 100 catheter use days. This rate is somewhat higher than the rate of 0.137 per 100 catheter days given by Clarke & Raffin (1990) in their review of the results from 51 studies with a total experience of 694,842 total catheter use days. A number of individual studies have reported equivalent or higher infection rates than were observed here (for example Press et al., 1984; Raviglione et al., 1989; Groeger et al., 1993). Comparison of infection rates between studies is difficult because of the lack of uniformity of the definitions of infection and because of the different patient populations studied.

**Exit Site Infection**

Exit site infection represented a much larger proportion of all catheter related infections in this study than has been observed elsewhere. In the prospective study by Benezra et al. (1988), for example, only 34 of 142 episodes of infection in 488 catheters were due to exit site infections. Similar ratios of exit site infections to other forms of catheter related infection have been reported by Pegues et al. (1992), Groeger et al. (1993) and Raviglione et al. (1989). In a review by Press et al. (1984) including 17 studies, 45% of all infectious complications were exit site infections, 20% were tunnel
infections and 34% were catheter related septicaemia. Thus the proportion of exit site infections observed in the current study (33 of 40 infections or 82%) is greater than expected.

Exit site cultures performed when clinical infection was observed showed a preponderance of gram positive organisms (see Table VI, page 53), particularly Staphylococcus aureus (30%) and coagulase negative staphylococci (35%). A similar preponderance of staphylococci has been observe in other studies of exit site infection (Groeger et al., 1993).

The determination of catheter exit site infection was based on the description of clinical signs recorded in the clinical record. In this study the notation within the clinical record of any degree of erythema, exudate, or tenderness was sufficient to lead to the designation of exit site infection. It is possible that the recording of trivial erythema at the catheter site by clinical staff could have lead to an excessive determination of cases of exit site infection. The nursing staff caring for these catheters routinely observed the exit site on a daily basis and exhibited a high index of suspicion for catheter related infection. The frequency of catheter related infection may therefore have been overestimated in this study because the retrospective study design and the broad clinical definition of exit site infection used.

A potential bias may result from the effect of regular observation of catheter exit sites for patients cared for as inpatients within the Hospital compared to the relatively infrequent observation of catheters in ambulatory patients with Hickman catheters being cared for at home. Patients with leukaemia, in particular, are more likely to be treated as inpatients.

These data show that exit site infection was a significant clinical problem, leading to substantial catheter loss in the study population. The frequency of exit site infection was higher than has been generally reported. The increased incidence of exit site infection was responsible for the somewhat high overall rate of infection per 100 catheter days of 0.28.

Subcutaneous Tunnel Infection

Only 3 subcutaneous tunnel infections were observed. These infections were somewhat less frequent than observed in other studies (for example Benezra et al., 1988). Two of these infections occurred very early after insertion suggesting insertion technique may have been important. Both of these
catheters were lost. Most studies have shown a poor salvage rate of Hickman catheters with subcutaneous tunnel infection. The limited data from this study are consistent with these findings.

Hickman Catheter Related Septicaemia

In this study, catheter related septicaemia was observed to complicate 11 catheters of which 7 were removed. In addition a further 5 catheters were lost for suspected infection. As discussed in Section 5 (page 24), the outcome from catheter related septicaemia may improve in some circumstances with early catheter removal, particularly when fungaemia or *Staphylococcus aureus* infection is present.

Only 3 of the 12 catheters removed because of proven or suspected catheter related septicaemic infections in this study were infected with *Staphylococcus aureus*. There were no episodes of catheter related fungaemia leading to catheter failure. Thus, although the incidence of catheter related septicaemia was relatively low in the study cohort, the outcome in terms of the number of Hickman catheters which failed, is disappointing. Arguably 9 of the 12 removed catheters were potentially salvageable, although probably not all of the infections would have responded adequately to antibiotic therapy with the catheter *in situ*. An assessment of the adequacy of the treatment given for catheter related sepsis is beyond the scope of this study. There were no deaths observed due to catheter related septicaemia. Although the numbers of catheters involved is small, it is possible that the removal of some of these catheters may not have significantly contributed to the resolution of the catheter-related infection. Possible premature removal of Hickman catheters because of suspected infection has been noted by Stansilav *et al.* (1987) in a retrospective study.

The microbiological isolates from blood (Table VIII, page 56) and from Hickman catheter tips (Table IX, page 58) demonstrate the extremely important role of gram positive organisms in catheter related septicaemia. Not surprisingly, the widespread use of the devices has been associated in a shift in the distribution of causative organisms in patients with neutropenic sepsis towards coagulase negative and positive staphylococci (Lazarus *et al.*, 1983; Gibson *et al.*, 1994).
Venous Thrombosis and Hickman Catheter Malfunction

Malfunction or thrombosis were observed to complicate 29% of all catheters, a slightly higher complication rate than was observed due to infection. Bagnall et al. (1989) in their study in a paediatric population, reported an incidence of catheter malfunction of 31%. In adults with solid tumours, similar rates of malfunction have also been observed (Cassidy et al., 1987).

Venous thrombosis was detected complicating 8% of catheters. The frequency of thrombosis observed elsewhere has ranged from 2.6% to 14% in studies where upper limb venography was only performed when patients were symptomatic or when the catheter was malfunctioning (Cassidy et al., 1987; Johnston et al., 1989; Beers et al., 1990; Puel V et al., 1993).

One patient within the study cohort suffered from clinically apparent pulmonary embolism after developing catheter related subclavian vein thrombosis. The true incidence of pulmonary embolus due to Hickman catheter related thrombosis remains uncertain (Leiby et al., 1989).

Eighteen catheters were lost because of malfunction or thrombosis compared to 23 catheter failures due to suspected or proven infection. Thus malfunction and thrombosis were major complications in the study cohort in terms of catheter loss. All detected cases were symptomatic or had poor catheter function. For patients with thrombosis of a major vein, the catheter was usually removed and intravenous heparin therapy provided. Attempts were made to salvage blocked catheters with the passage of intraluminal wires and, on 4 occasions, streptokinase therapy. Urokinase was not used during the study period. Some of the 8 catheters which failed due to blockage in the absence of venous thrombosis may have been successfully salvaged with more frequent exhibition of low dose thrombolytic therapy.

Local infusions of urokinase or tissue plasminogen activator may speed the resolution of venous thrombosis and permit retention of perhaps one half of the associated catheters (Fraschini et al., 1987; Rodenhuis et al., 1993). Some authors recommend removal of catheters in the presence of symptomatic venous thrombosis (Hill & Berry, 1990). This was the practice followed during the present study, with the exception of 2 Hickman catheters treated with, and salvaged by, streptokinase infusions.
Hickman Catheter Migration or Dislodgement

Eleven catheters were complicated in this way and 8 (5% of all catheters) were lost. Thus although migration or dislodgement was a relatively infrequent event, catheter failure due to these complications was important. Other studies have shown similar rates of catheter failure due dislodgement/migration (Reed et al., 1983; Harvey et al., 1986; Hughes et al., 1989). Dislodgement is a frequent cause of failure of Hickman catheters in paediatric populations, particularly among very young children (Mirro et al., 1990).

In this study, 2 catheters were lost soon after insertion because of accidental dislodgement in patients who were confused due to delirium related to their underlying illness. The occurrence of these complications emphasises the need for vigilance in the care and use of these catheters in order to minimise the risk of accidental loss.

Other Complications of Hickman Catheter Insertion and Use

Only very infrequent and mild acute complications of catheter placement were observed. Pneumothorax complicating catheter insertion was not observed in this study despite rates of up to 7.5% reported in other studies also using a percutaneous insertion technique (Lameris et al., 1990). Only 1 instance of accidental arterial puncture was observed. Similar studies have observed accidental arterial puncture rates of up to 6% (Wisborg et al., 1990). Extravasation of infused drugs was also not observed during the study period, although a case of severe cytotoxic drug extravasation due to back-tracking of infusate around a Hickman catheter has subsequently been reported from Woden Valley Hospital.

Patient Diagnosis and Hickman Catheter Complications

The nature of the malignant disease for which the Hickman catheter is placed has been shown in a number of studies to influence outcome. Patients with acute leukaemia or other disorders in which prolonged neutropenia is frequently seen, such as after autologous bone marrow transplantation, have been observed to suffer higher rates of catheter related septicaemia (Press et al., 1984; Ranson et al., 1989; Groeger et al., 1993). Patients with solid tumours, particularly carcinomas, have been reported to experience higher rates of catheter thrombosis (Anderson et al., 1989).
In the current study, the diagnosis of acute leukaemia was associated with a relative risk of catheter related septicaemia of 3.11. The severity and duration of neutropenia was not assessed within this study, however patients with acute leukaemia receiving induction chemotherapy routinely experience substantially more intense neutropenia than patients with solid tumours or lymphoma. The Hickman catheters in such patients might be expected to be used more frequently than in patients without acute leukaemia, reflecting the intensity of supportive care, including blood product infusions, employed in this group. Mucositis is also a common accompaniment of intense leukaemia induction therapy, possibly increasing the risk of translocation of an infecting organism to the catheter. Data describing the severity of mucositis and the relative frequency of catheter use were not available in this study. Acute leukaemia was not associated with an increased incidence of exit site or catheter tunnel infection.

The excess of Hickman catheter related sepsis was not accompanied by an excess risk of catheter failure in patients with acute leukaemia. The diagnosis of acute leukaemia was not associated with a shorter time to failure in a Cox proportional hazards model.

The patient diagnosis was not related to the risk of catheter related thrombosis or catheter malfunction in this study. Patient diagnostic group was likewise not a significant predictor of time to malfunction in the Cox proportional hazards model.

**Patient Gender**

A previous study of Hickman catheter use has associated male gender with Hickman catheter infection (Claessen et al., 1990). In the current study male gender was associated with a relative risk of exit site infection of 2.6. Male gender was not associated with any observed increase in risk of catheter related septicaemia, or of catheter malfunction, thrombosis or dislodgement. The observed excess risk of exit site infection led to an excess of catheter failures in male patients. Male gender was associated with a relative risk of catheter failure of 2.02. The time to catheter failure was shorter for male patients, and this was confirmed in a Cox proportional hazards model of time to catheter failure.

The majority of previous studies have not identified gender as an independent risk factor for Hickman catheter complications. In this study it
was specifically exit site infection which was observed more frequently in male patients, and this effect was sufficiently strong to lead to a substantial increased risk of catheter failure, even when potential confounding factors such as disease group and obesity were controlled in a Cox multivariate model.

The way in which male gender caused the observed increase in exit site infection is unclear. Reed et al (1983) have suggested physical activity may cause the collection of fluid under semipermeable dressings (as used in the study cohort) and that this process may lead to exit site infection. Perhaps ambulatory male patients were more likely to be physically active. It is also possible that the standard of catheter care varied on the basis of gender. Some catheter care was performed at home by a relative of the patient, often the spouse, after a period of instruction by professional staff. This form of care occurred when a suitable carer was available. Anecdotally, this was most often the female carer of a male patient. One can speculate that female patients may have received better catheter care simply because their male spouses was not so readily trainable to replace professional community nurses. Data relating to the identity of the person performing catheter care was not collected as part of this study. There is ample evidence to suggest that the quality of nursing care is a major determinant of catheter related infection (Keohane et al., 1983). The adequacy and frequency of Hickman catheter exit site care should be carefully followed in quality assurance programs and future studies of catheter related infection.

**Obesity**

In this study the presence of obesity, as defined, was associated with a relative risk of catheter migration/dislodgement of 4.5. Anecdotal reports of catheter migration or dislodgement in obese patients exist (Heyd & Rosser, 1991). Similarly, loss of Hickman catheters has been reported due to pendulous breasts (Moorman et al., 1987). The migration is almost certainly due to mechanical factors related to the subcutaneous tunnel. The Hickman catheters were inserted with the patient supine. The catheter is tethered by the Dacron subcutaneous cuff. In obese patients, if the catheter is not very carefully placed, the catheter tip is simply withdrawn from the superior vena cava when the patient stands after insertion. Due to the relatively mobile subcutaneous tissues of obese patients the catheter remains, throughout its
life, at a greater than normal risk of catheter tip migration to an unsatisfactory position.

Obesity was not associated with an increased risk of infection in this study, although this has been reported elsewhere (Newman et al., 1993). No increase in the risk of catheter malfunction due to obesity was observed. Despite the increased risk of catheter migration/dislodgement observed, there was no overall increase in the risk of catheter failure in obese patients. However, in the Cox proportional hazards model, the body mass index was a statistically significant predictor of time to catheter failure. A hazard ratio for catheter failure of 1.1 for each unit increase in body mass index when insertion site and gender were controlled was observed. In a similar proportional hazards model for time to poor function, body mass index was also a statistically significant predictor variable.

The findings in this study suggest an important increase in risk for adverse outcomes from Hickman catheters as the body mass index rises. This risk factor for Hickman catheter complications has not been widely studied to date. Possibly some of the complications observed may have been preventable with more careful selection of the catheter exit site by the inserting operator. However, it appears that Hickman and other catheters which feature a subcutaneous tunnel may be less useful devices in obese patients. In particular, non tunnelled non cuffed catheters may be preferable in these circumstances. Further studies of the influence of body mass index and central venous catheter complications should be undertaken to extend the findings in this study. The measurement of body mass index in future prospective studies of central venous access devices is recomended.

Site of Catheter Insertion and Catheter Tip Position

The selection of the left subclavian vein for Hickman catheter insertion, rather than the right side, was associated with a relative risk of venous thrombosis of 4.38. There was also an elevated risk of catheter malfunction. A suggestion that thrombotic complications may follow left sided catheter insertion was initially made by Brown-Smith et al. (1990). Puel et al. (1993) have reported a high incidence of venous thrombosis in patients with left sided catheters where the catheter tip was inadvertently positioned high in the superior vena cava. The current study confirms and strengthens these findings.
Catheter malfunction was somewhat more common in this study when the measured catheter tip position was high within the vena cava. The time to malfunction was also shorter when catheters ended high within the superior vena cava. However, when catheter position was entered into a Cox proportional hazards model for time to malfunction it was not a significant explanatory variable with insertion site, body mass index, and the number of catheter lumens controlled. Venous thrombosis was not more frequent in patients with "high" catheters. Although the findings are suggestive, this study does not necessarily support the findings of Stanislav et al. (1987) where high catheter tip position did lead to venous thrombosis.

The insertion site (left versus right) was not associated with an increased risk of infection or migration. Left sided insertion was associated with a relative risk of catheter failure of 2.3. The excess of catheter failure for left sided insertions was due to thrombosis. The insertion site was a significant predictive factor for time to catheter failure and time to catheter malfunction in both Cox proportional models used in the study.

Left side catheters follow a more acute arc within the left subclavian vein, innominate vein, and upper superior vena cava than right sided catheters. This leads to the catheter tip abutting the lateral wall of the vena cava (Figure 7). Irritation of the intima of the vena cava by the catheter and by irritant infusates could lead to platelet aggregation and the initiation of thrombosis. The influence of catheter insertion site might be expected to vary depending on the position of the catheter tip within the superior vena cava of right atrium. No interaction between these factors was detected within this study, although the number of initial left sided catheters was small (only 21) and such a relationship is not excluded.

The results of this study suggest that left sided Hickman catheters should be avoided if possible. Based on the study of Puel et al. (1993), left sided Hickman catheters, if inserted at all, should be positioned so that the catheter tip is within the right atrium in order to reduce the risk of venous thrombosis. Insertion site is an important factor requiring control in any future studies of catheter related thrombosis.

Double Lumen Catheters

Single lumen Hickman catheters have been observed to have a lower rate of infection when compared to double lumen catheters is several retrospective
studies (for example Henriques et al., 1993). In the current study the number of catheter lumens was not a risk factor for any form of catheter related infection.

Catheter malfunction was more frequently observed in this study with double lumen catheters. Moreover the number of catheter lumens was predictive of time to catheter malfunction in a Cox proportional hazards model. The risk of venous thrombosis was not increased with the use of double lumen catheters. The study design did not allow for the assessment of the function of each lumen in double lumen catheters. Double lumen catheters have a greater external diameter than single lumen catheters and this could be a factor in the formation of a fibrin sleeve at the catheter tip, leading to malfunction (Horattas et al., 1988).

Based on the results of this study and others, double lumen Hickman catheters should be avoided unless the provision of more than one lumen is essential.
Figure 7
Chest radiograph showing a left sided Hickman catheter demonstrating the acutely curved course taken on entry of the superior vena cava (arrow) and the close apposition of the catheter tip to the lateral caval wall.
11. CONCLUSIONS

The observed median duration of catheter use of 55 days and the catheter failure rate of 32% are similar to the findings of other studies of Hickman catheter use. Adverse events were more frequent among individuals with high body mass index, among males and in patients with leukaemia. Left sided catheter insertion was associated with a high risk of thrombosis and should be avoided if possible.

The results emphasise the need for the judicious use of these devices, particularly for the high risk groups. Non-tunelled catheter types may be preferable for obese people to reduce the risk of catheter displacement. The need for explicit protocols for catheter maintenance and use, and also for the management of complications is apparent. Special emphasis and advice regarding exit site care should be given to male patients. Maximal sterile precautions during catheter use are justified for patients with leukaemia.

Further research, aimed at refining practice in this area should be undertaken. Newer intravascular devices, such as non tunelled silastic catheters, and antibiotic impregnated cuffs should be tested, preferably in randomised trials. Studies on the relative cost-effectiveness of fully implanted ports are also required. Prophylactic antibiotics at the time of insertion or as regular "flushes" require careful evaluation, particularly in view of the potential risk of stimulating microbial resistance. Such studies will provide the stimulus for improvement to be made in the management of patients requiring durable venous access. Based on the findings of this study, the patient's BMI, gender, and the site of catheter insertion should be recorded, along with the underlying disease type, in new studies of Hickman or similar catheters.

This study, with others, demonstrates the imperfection of the currently available devices and methods. In people with a major illness such as cancer or leukaemia, Hickman catheter complications may seem to be mostly only of nuisance value. Clinicians easily underestimate the frequency and severity of these types of adverse events. Prospective studies of a selected "series" of patients in which a new device or technique is tested tend to systematically underestimate the risk of adverse events which will be observed when the technology is subjected to general, non-trial, use. The adverse events observed in this study, particularly nosocomial catheter
infection and catheter related thrombosis, form part of a silent epidemic of iatrogenic illness which has accompanied the transfer of new intensive medical therapies into general use.

Ongoing, high quality, institutional surveillance of the complications of these devices should be seen a part of standard care in patients with malignant disease. Such surveillance would then become a criterion for any proposed accreditation process developed for institutions treating cancer. Consolidation of information across a group of collaborating institutions might be expected to lead to the timely identification of group wide trends and also of problems occurring within a single treatment centre. Such a program could lead to a greater dividend in terms of quality of life and cost savings than many technologically complex clinical innovations under current investigation.
REFERENCES


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ADDENDUM

1. Clinical pulmonary embolus and Hickman catheters:
In this study only one patient was observed to develop a clinical pulmonary embolus which may have been associated with Hickman catheter related thrombosis. Clinical pulmonary embolus was therefore observed to complicate 0.7% of all Hickman catheters.

2. Adherence to protocols for Hickman catheter insertion and care:
Protocols were in place during the study period for the insertion and care of Hickman catheters. Adherence to these protocols was not assessed in the study due to the lack of available data in the records reviewed.

3. Definition of catheter related septicaemia:
The definition of catheter related septicaemia was modelled on that of Mirro et al. (1989). Cases of septicaemia were considered catheter related if they occurred: (1) in the absence of an exit site or tunnel infection which resolved within 48 hours of removing the catheter without the addition of antibiotic therapy; OR (2) with a positive culture of blood drawn from the catheter but with a simultaneous negative blood culture obtained from venipuncture; OR (3) the same organism cultured from blood and from the catheter tip after catheter removal. These presence of signs of infection at a distant site did not exclude catheter related septicaemia. This definition has been widely applied, particularly in retrospective studies. Some studies, such as Benezera et al. (1990) have excluded cases of septicaemia where there are signs of infection at a distant site. These studies have been prospective and have usually employed quantitative blood culture methods. It is possible that the definition of Mirro et al. might lead to an over estimate of the frequency of Hickman catheter related septicaemia. It was not possible to estimate the size of this effect (if any) from the current study.

4. Association between catheter infection, nature of pathogen and concurrent antibiotics or distant infection:
Due to the nature of the data sources used for the study accurate data describing distant infection and antibiotic use were not available. The association could not, therefore, be examined in this study.

5. Increased incidence of Gram positive infection in patients with neutropenia:
In this study, and others, Gram positive organisms account for more than 50% of pathogens causing Hickman catheter related infection. As Hickman catheters and similar devices have been used more widely in patient populations at risk for neutropenia, there has been a trend towards Gram positive organisms becoming more frequent pathogens in this group. This trend has been documented recently in Australia (Gibson et al., 1994).