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Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting

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ABSTRACT

Purpose: Patients with febrile neutropaenia (FN) can be stratified according to their risk of significant complications, allowing reduced intensity therapy for low risk (LR) episodes. Serious events are very rare in low risk episodes making randomised trials difficult. Introduction of new evidence-based guidelines followed by re-auditing of the outcome is an alternative strategy.

Methods: New guidelines for the management of LR FN were implemented in 4 specialist paediatric oncology centres (POCs) and in their associated shared care units (POSCUs). All patients commenced empirical intravenous antibiotic therapy and after 48 h those with blood culture negative episodes designated LR were eligible for discharge on oral co-amoxiclav. Prospective data collection on FN episodes in all treatment centres was undertaken over a 1-year period.

Results: Seven hundred and sixty two eligible episodes of FN were recorded in 368 patients; 213 episodes were initiated in POCs and 549 episodes were initiated in POSCUs. In 40% of episodes no clinical or microbiological focus of infection was found. At 48 h, 212 (27%) episodes were classified as LR and 143 of these (19%) were managed on the LR protocol. There was a low hospital readmission rate (8/143 episodes; 5.6%), no intensive care admissions and no deaths in LR episodes. Almost all LR episodes (209/212) occurred in the shared care setting.

Conclusions: Rapid step-down to oral antibiotics was a feasible and safe management strategy for LR FN in the shared care setting in England.

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1. Introduction

Febrile neutropaenia (FN) remains a frequent cause of hospitalisation in children treated for cancer. With good supportive care, mortality during FN is now of the order 1–3%.[1,2] Less than 50% of children show a clinical or microbiological focus of infection during FN[1] and the incidence of severe adverse outcomes such as intensive care admission and death is low.[1,2] Thus the focus of care has shifted to management by risk stratification, potentially allowing a reduction in the intensity and/or duration of therapy in low risk (LR) patients[3,4] but it is clear, at least in the United Kingdom (UK), that LR management strategies have not been widely used.[5,6]

Validated risk assessment strategies have been developed in adults, using 'serious medical complications' as the outcome measure.[7–9] In children, risk prediction studies have focussed on bacteraemia or significant bacterial infection as the main outcome measures[10–17] and there remains no validated risk assessment predicting clinical outcome.[4] However, clinical variables defining LR FN in children can be inferred from the literature on risk prediction and from the significant number of small studies of LR strategies in children with FN.[3,4] Cytokine levels and innate immune markers in future may contribute to risk assessment.[18,19]

Studies of LR management strategies have been conducted in specialist paediatric oncology centres: there are no previous reports of LR strategies implemented in a broader setting. This study assessed the feasibility and safety of a conservative, LR FN strategy in 4 UK specialist paediatric oncology centres (POCs) and their associated shared care units (POSCUs) using readmission rate, intensive care admission and death as the main measures of adverse outcome.

2. Methods

The 4 POCs in London share care with over 50 POSCUs based in general hospitals. The role of the POC and POSCU in supportive care has been previously described.[20] Common supportive care guidelines are utilised.

From 01/04/2004 the management protocol for FN included a reduced intensity treatment strategy for LR episodes. A prospective audit was undertaken to monitor outcome in the period 01/04/2004–31/03/2005.

The definition and evaluation of FN were as previously described.[20] Neutropaenia was defined as absolute neutrophil count (ANC) $< 1.0 \times 10^9$/L and fever as a single temperature $\geqslant 38.5$ °C or sustained temperature over 4 h of >38 °C. All children with FN were hospitalised and received empirical intravenous piperacillin/tazobactam 90 mg/kg × 4/d and once-daily intravenous gentamicin (7 mg/kg) or amikacin (20 mg/kg). Patients with persistent fever after 96 h of antibiotics commenced intravenous amphotericin B (0.3 mg/kg) or liposomal amphotericin (1 mg/kg).

A checklist of risk factors was completed at the start of each FN episode and 48 h later (see Table 1). Episodes were designated LR if no risk factors were identified at either timepoint; all other episodes were designated standard risk (SR). Fever at 48 h did not exclude from the LR strategy.

Table 1 – Risk factors excluding from low risk protocol.

Admission and 48 h assessment
Age
<1 year
Associated medical conditions requiring hospitalisation
Shock or compensated shock
Haemorrhage
Dehydration
Metabolic instability
Altered mental status
Pneumonitis
Mucositis (unable to tolerate oral fluids or requiring IV analgesia)
Respiratory distress/compromise
Perirectal or other soft tissue abscess
Rigors
Irritability/meningism
Organ failure
Cancer associated co-morbidities
ALL at diagnosis/relapse <28 d
ALL not in remission >28 d
AML
Infant ALL
Intensive B-NHL protocols
Haemopoietic stem cell transplant
Sequential high dose chemotherapy with PBSC rescue
History
Intensive care admission during last FN episode
Non adherence (social concerns or patient)
Inability to tolerate oral antibiotics
48 h Assessment only
Positive blood culture result at 48 h
ANC $< 0.1 \times 10^9$/L at 48 h
Child not clinically well at 48 h (clinician judgement)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; B-NHL, B cell non-Hodgkins lymphoma; BMT, bone marrow transplant; PBSC, peripheral blood stem cells; and ANC, absolute neutrophil count.

In LR episodes, patients could be discharged at 48 h taking oral co-amoxiclav until 48 h after resolution of fever (<37.5 °C). The dose of co-amoxiclav was: 0.8 ml/kg/d of 250/62 suspension in three divided doses (maximum 32 ml/d); or 625 mg tablet × 3/d if age > 12 years; or Augmentin Duo© suspension 400/57 0.3 ml/kg × 2/d aged 1–2 years, 5 ml × 3/d aged 2–6 years and 10 ml × 2/d aged 7–12 years. Children with penicillin allergy received clarithromycin or ciprofloxacin. The family was contacted by telephone at 72 h and the child was assessed at 96 h (at home by a community paediatric nurse or in hospital) for overall status, fever, vital signs and measurement of ANC. Patients remaining febrile (>38 °C) at 96 h were readmitted to hospital for intravenous antibiotics and an amphotericin preparation. Children could be readmitted at other times if concerns were raised.

The FN protocol was distributed to all relevant POCs and POSCUs in March 2004 and staff were invited to a project launch meeting. An educational presentation was distributed for use in the POSCUs. The lead consultant paediatrician in all 4 POCs and 54 POSCUs was invited to participate in data collection. A site facilitator was identified in each unit.

Patients were managed as LR or SR according to the defined management protocol. Risk factor checklists and details of symptoms and signs at presentation, culture and radiology results, nature and duration of antibiotics, days in hospital and risk assessment and management by risk stratification were collected for each episode of FN. We also collected data on readmission after early discharge in LR episodes, intensive care admission and death. Pseudoanonymisation of patient-identifying data ensured compliance with data protection guidelines. Data were not collected for episodes of FN that followed haematopoietic stem cell transplant.

All data were reviewed by 2 project investigators (J.C. and R.D.). Data were consolidated and analysed in an anonymous format using a purpose-built Microsoft Access database. The Local Research Ethics Committee at Great Ormond Street Hospital advised that the project did not require ethical approval.

As this was primarily an audit project, there was no formal power calculation. We anticipated around 1000 episodes of febrile neutropaenia in the audit period,[20] up to 25% episodes in the LR group[21] and a low readmission rate (<10%), no deaths and no intensive care admissions in the LR group.[22–24]

3. Results

Forty-three POSCUs and all 4 POCs participated. Data were received on 815 episodes from 4 POCs and 42 POSCUs. The data returns were compared against all episodes of FN that were documented as occurring in POC or POSCU in records of patients at the largest 2 POCs, giving an estimated return rate of 75%.

Fifty-three episodes (6.5%) were excluded from analysis (Fig. 1; 38, patient not neutropaenic; 11, insufficient data; 4, other reasons) leaving 762 eligible episodes in 368 patients (median 2.0 per patient, range 1–8). Acute lymphoblastic leukaemia (ALL) was the commonest diagnosis, accounting for 51% of patients and 50% of episodes (Table 2). Median age at first recorded FN admission was 5 years 7 months (range 1 month to 17 years 6 months).

Overall, 72% of episodes were initiated in POCSUs (Table 2). The distribution of diseases was different in POC and POSCU (Table 2), reflecting the practice of keeping most children on high risk treatment protocols (e.g. acute myeloid leukaemia and intensive B-non-Hodgkin's lymphoma protocols) at the POC for supportive care.[17]

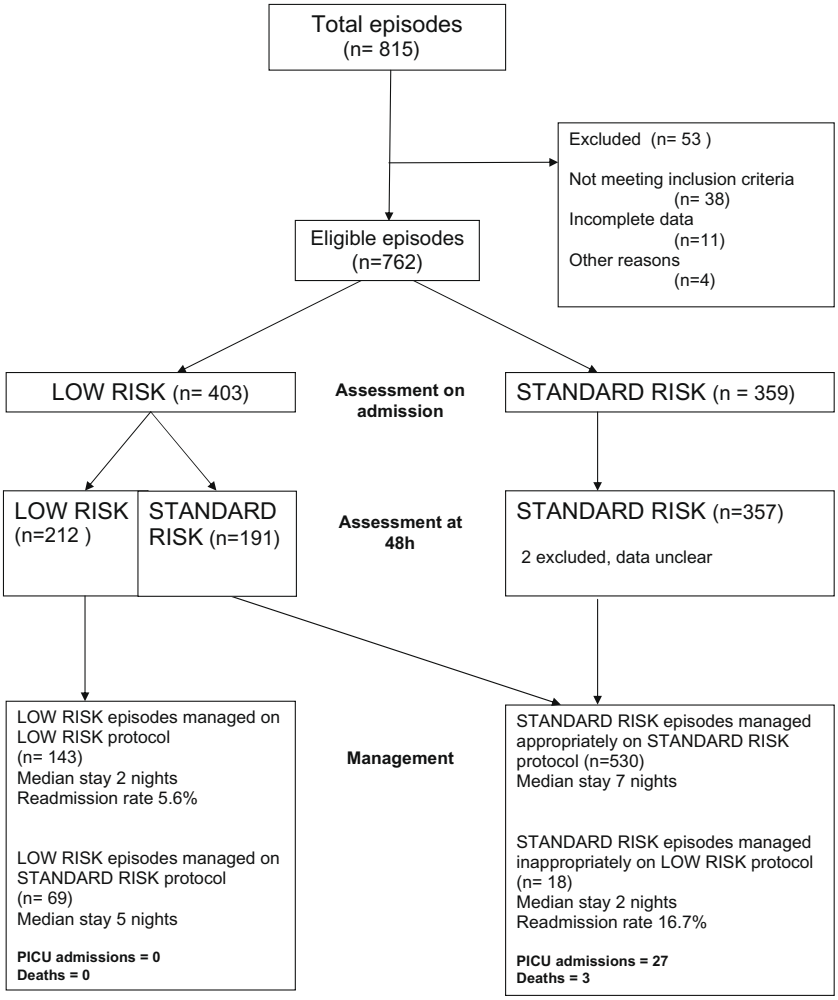

Fig. 1 – Episode flow. See text for details of risk assessment on admission and at 48 h and for low and standard risk management strategies.

Table 2 – Numbers of patients and episodes by diagnosis in POC and POSCU.

Diagnosis	No. of patients	Episodes initiated in POC	Episodes initiated in POSCU	Total episodes (%)
Acute lymphoblastic leukaemia	188	68	316	384 (50.3)
Acute myeloid leukaemia	33	89	11	100 (13.1)
Lymphoma	37	24	43	67 (8.7)[a]
Brain tumour	18	3	28	31 (4.1)
Bone tumour	20	3	36	39 (5.1)
Neuroblastoma	20	15	19	34 (4.5)
Wilm's tumour	14	4	31	35 (4.6)
Soft tissue sarcoma	12	2	25	27 (3.5)
Other	26	5	40	45 (5.9)
Total (%)	368	213 (28.0)	549 (72.0)	762

a Included 28 patients with non-Hodgkin's lymphoma (56 episodes), 8 patients with Hodgkin's lymphoma (9 episodes) and 1 patient with post transplant lymphoproliferative disorder (2 episodes).

3.1. *Infections*

There was symptomatic evidence of infection other than fever in 50.9% of episodes (Table 3). Evidence of infection was documented on clinical and/or radiological examination in 41.1% episodes with data on admission (Table 3) and microbiological evidence of infection was found in 325 episodes (42.3%). Forty percent of all episodes and 58% of POSCU episodes with complete data had neither a clinical/radiological nor a microbiological focus of infection (data not shown).

Two hundred and sixty one bacterial or fungal isolates were documented in presenting blood cultures in 223 episodes (29.3%; Table 4). A further 58 new positive blood culture isolates were documented in 55 episodes (7.2%) from cultures taken more than 48 h from the onset of FN. Fifty-four episodes (7.0%) were associated with positive urine, skin or other cultures/microbiology from admission and 29 (3.8%) episodes were associated with new positive microbiology from sites other than blood later than 48 h. Details of blood culture isolates are given in Table 5. Full information about species of isolates was not available on all the data collection sheets.

3.2. *Risk assessment and management by risk stratification*

Completed risk factor checklists from admission and 48 h were received in 721 episodes (94.6%). Patient flow including risk assessment and management by risk stratification is shown in Fig. 1.

Four hundred and three episodes (52.8%) were designated LR on admission (POCs, 7 (3.3%); POSCUs, 396 (72.0%)). The commonest reason for exclusion from LR in POCs was underlying diagnosis (147; 69.0%) and in POSCUs was co-existing medical conditions (46; 8.4%) or diagnosis (38; 6.9%).

In 191/403 episodes, risk assignment changed from LR to SR at 48 h (Table 6), including 92 episodes with positive admission blood cultures. Only 3 POC episodes were assessed as LR both on admission and at 48 h.

One hundred and sixty one episodes were managed on the LR strategy (143 episodes appropriately managed as LR and a further 18 episodes where the episode was classified as SR). Sixty nine of 212 episodes potentially eligible for LR management (9.0%) were managed as SR for the following reasons: clinical decision (35); ongoing fever (6); confusion over ANC threshold for LR strategy (4) or unclear (24).

3.3. *Outcome of patients treated as LR*

Median inpatient stay was 2 nights prior to discharge on the LR protocol (range 1–4). Most children were discharged on oral co-amoxiclav (114/161; 71%, data missing in 8 episodes) although an alternative oral antibiotic (7 episodes) or an intravenous antimicrobial (7 episodes) was sometimes utilised. No antibiotic was prescribed if the child had been apyrexial for 48 h already before discharge (24 episodes). The median duration of oral antibiotics was 5 d (range 0–8) in 136 episodes with data (5 d for LR episodes and 5 d for SR episodes managed as LR). The median total (intravenous and oral) antibiotic days were 7 (range 2–20) in 156 episodes (7 days for LR episodes and 7 d for SR episodes managed as LR).

During 17/161 episodes managed as LR (15 LR, 2 SR managed as LR) the child required hospital review before the planned 96 h time point (3, parental concern; 3, persistent fever and 11 no reason given) and 5 of these were readmitted (3 LR, 2 SR managed as LR). At the 96 h review, almost all episodes with data had ANC $\geqslant 0.1 \times 10^9$/L (102/110, 93%).

In total there were 11 readmissions to hospital (6.8%), including 8/143 LR episodes (5.6%) and 3/18 (16.7%) SR episodes inappropriately managed as LR. Median inpatient stay was 2 nights in both groups prior to initial discharge. The median number of days between first discharge and readmission was 1 (range 1–2) in the 5 episodes for which data were

Table 6 – Reasons for change from low to standard risk at 48 h in episodes assessed as standard risk on admission.

Reason for change	No. of episodes
New exclusion criteria on risk stratification at 48 h	25 (13.1%)
Positive blood culture only	69 (36.1%)
ANC < 0.1 only	47 (24.6%)
Positive blood cultures plus ANC < 0.1	23 (12.0%)
Other clinical reasons	10 (5.2%)
No reason given	17 (8.9%)
Total	191

available. Causes of readmission in the 11 episodes were clinical deterioration (6), persistent fever (3), parental concern (2), inability to tolerate oral antibiotics (1) and development of Herpes Zoster (1). All patients readmitted to hospital made an uneventful recovery with a median of 4 nights spent in hospital following readmission (range 1–16). There were no positive blood cultures in readmitted patients.

There were no intensive care admissions and no deaths during any episodes assessed or managed as LR.

3.4. *Outcome of patients managed as SR*

548 episodes were assessed and managed as SR. A further 69 LR episodes were managed as SR. The median inpatient stay for all these episodes was 7 nights (range 1–105); 5 nights in POSCUs and 11 nights in POCs. Median inpatient stay for episodes assessed as LR but managed according to the SR protocol was 5 nights compared to 7 nights for patients assessed and managed as SR. Median duration of antibiotics was also shorter in patients assessed as LR but managed as SR (5 d versus 8 d).

PICU admission was recorded in 27 episodes (3.5%), all assessed and treated as SR (17/213 POC episodes, 10/549 POSCU episodes). Three deaths were captured in the study, one due to disease progression and 2 late deaths from infection (both patients were admitted to PICU). We also traced 3 further deaths from infection in POCs in SR episodes that were not captured in the audit. Our apparent death rate from infection was about 5/1000 episodes (0.5%).

4. Discussion

This study was part of an ongoing attempt to rationalise therapy in children with FN.[5,6,20] Treating a significant proportion of patients with outpatient antibiotic therapy (OPAT) could have a significant impact on the quality of life and on the cost of care. Step-down strategies for LR FN are now well documented in the adult literature although clear evidence of equivalence to intravenous strategies in children is lacking through the absence of large, well-designed trials. As serious events in LR episodes of FN are rare, the numbers of children required to compare outcomes of different management strategies make such trials extremely difficult to conduct. Analysis of our previous data led us to conclude that a randomised study demonstrating equivalence of different FN management regimens was not feasible. We therefore decided to introduce a new step-down strategy based on the previous data and to audit the outcome.

Accurate identification of LR episodes is very important so that OPAT does not compromise safety. The risk criteria adopted in our new guidelines for the management of LR FN were therefore very conservative.[3,4] In addition, we excluded certain diagnostic groups (e.g. AML, B-NHL) with a known high risk of infection after intensive chemotherapy although most episodes in these children would be excluded from the LR group for other reasons (e.g. neutrophils $< 0.1 \times 10^9$/L or comorbidities such as mucositis). As the initial 48 h of FN management was identical irrespective of first risk assessment and the strategy allowed 48 h of observation in hospital with blood and other culture results available before final allocation of risk group, we chose not to use neutrophil or monocyte count (predictors of significant or invasive bacterial infection) as part of the initial risk stratification.

The only study attempting to identify children with severe infectious complications of FN was a retrospective study from Brazil in which patients were routinely given empirical ceftriaxone or cefipime monotherapy.[25] FN was associated with a severe infectious complication in 32% of episodes, 30% of patients were admitted to the intensive care unit, and 4% of patients died from infectious complications. Gram negative isolates predominated (54% of isolates). Thus the patient and episode characteristics differed significantly from this study. Paediatric FN studies would benefit from a validated algorithm for predicting adverse outcome and development of such an algorithm remains an important goal.

Despite the limitations of our study, the low readmission rate and the absence of intensive care admissions and deaths in LR episodes reported here appear to support the safety of the risk assessment and management strategy that we implemented and then audited. It is likely that most of the episodes that were not captured in the audit occurred in the POSCU setting, suggesting that the incidence of low risk episodes was under-reported in this study. However, we had no recorded episodes of transfers into POCs or intensive care admissions among children that started on the low risk strategy in the POSCU setting; these episodes would have been captured in the POC. We have also shown that resolution of fever is not an essential prerequisite for step-down at 48 h.

It was disappointing that only 19% (143/762) of all episodes were managed on the LR strategy even though 28% of episodes were assessed as LR at 48 h. This reflects our cautious approach to the introduction of the new guidelines, with many children excluded from the LR group. This is similar to a report of a step-down strategy, with risk stratification applied on admission, where 26% of patients were potentially eligible for LR management but only 15% were managed in this way because of clinical deterioration, persistent fever, rapid resolution of fever and neutropaenia or preference of physician or family.[21]

In our study the commonest reason (35/69) for failure to manage according to the LR strategy was ‘clinical decision’. The LR strategy was utilised more widely in some POSCUs than in others and clinicians may have been wary of the strategy. This is likely to improve as data on the safety of the approach are disseminated.

The risk assessment may have been more conservative than necessary; 24% of episodes assessed as LR on admission changed to SR at 48 h because ANC was $<0.1 \times 10^9$/L (Table 6). ANC primarily predicts invasive bacterial infection but in these episodes admission blood cultures were negative. It may be possible to safely include these episodes in the LR strategy but stepwise changes would need careful prospective monitoring. Ninety-two children changed to SR because of positive blood cultures with or without another risk factor (Table 6) .The rate of positive blood cultures was high in this study (29%) but is similar to that recorded in our previous audit of shared care FN episodes in London[20] and may reflect the universal usage of central venous catheters and the overdiagnosis of coagulase negative Staphylococcal infection, since the protocol did not require more than one positive culture for this diagnosis to be made.

Co-amoxiclav was chosen to cover common paediatric infections, including respiratory infections, whilst retaining some gram negative cover. Studies of oral antibiotics from the onset of FN have used ciprofloxacin with co-amoxiclav.[26,27] In this study potentially serious gram negative bacteraemia had been virtually excluded by the timing of step-down and it could be argued that such LR episodes may not require continued oral antibiotics at all. However, there are no reports of discontinuation of all antibiotics at 48 h in patients with continued fever.

The LR strategy was applied in the setting of a complex network of care in specialist and non-specialist hospitals. To our knowledge, this is the first study to demonstrate that risk assessment and a step-down strategy can be applied in non-specialist hospitals. Important components were common supportive care guidelines, established care pathways and easy access of POSCUs to advice from the specialist unit. Initial education and ongoing support to the POSCUs were necessary to underpin the strategy. Management appeared appropriate in the vast majority of patients, implying that physicians had understood the concepts involved. The higher readmission rate among children inappropriately managed on the LR strategy was a concern; it is an important safety issue that reduced intensity therapy should be utilised only when episodes meet agreed criteria.

Reducing inpatient therapy in LR FN has the potential to reduce the costs of care, to reduce the risks of nosocomial infection and antimicrobial resistance and very importantly to reduce the 'social impact' of FN on the child and family. Even so, LR strategies are not widespread in paediatric practice in the UK.[5] The significantly improved audit return rate compared to that in our previous study[20] suggested an enthusiasm on the part of POSCUs to utilise risk stratification. A survey has suggested that the strategy is acceptable to patients and staff.[28]

We did not attempt a formal health economic evaluation but other studies have suggested cost savings from outpatient or step-down therapy for FN.[29,30] We have previously documented a median inpatient stay of 5 d for POSCU episodes of FN managed on intravenous antibiotics before the introduction of the LR strategy[20] suggesting a saving of up to 3 bed days for each LR episode. Since almost 40% of POSCU patients were potentially eligible for the LR strategy, its wide application could have a considerable impact on bed usage in the POSCU.

We have shown that a conservative step-down strategy for LR FN can be safely implemented in a UK shared care setting. Such strategies should be encouraged as a way of rationalising care in LR FN. The Supportive Care Group of the UK Children's Cancer and Leukaemia Group has now produced framework guidelines for POCs to help the design of local FN management protocols. An audit is planned to assess the impact of these guidelines on practice. Shared care is not practiced in all European countries, but step-down strategies for selected patients are potentially appropriate in most settings, provided oncology staff are familiar with the concepts and patients have rapid access to hospital if their condition changes.

Although randomised trials in LR FN remain the gold standard, the patient numbers required make such a study unlikely ever to be performed. We have shown that audit, cautious implementation of new guidelines, followed by re-audit is a safe method to improve care in children with FN.

Conflicts of interest statement

None declared.

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Appendix 1

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Chelsea and Westminster Hospital
Ealing Hospital
Kent and Canterbury Hospital
Queen Elizabeth the Queen Mother Hospital
Conquest Hospital
Eastbourne District General Hospital
Epsom General Hospital
St Helier Hospital
Frimley Park Hospital
King's College Hospital
Kingston Hospital
William Harvey Hospital
Mayday University Hospital
Medway Maritime Hospital
St John's Hospital, Chelmsford
St Peter's Hospital, Chertsey
Newham General Hospital
North Middlesex Hospital
Northwick Park Hospital
Princess Alexandra Hospital, Harlow
Queen Mary's Hospital, Sidcup
Royal Free Hospital
Royal Surrey County Hospital
Southend Hospital
St George's Hospital, Tooting
St Mary's Hospital, Paddington
East Surrey Hospital
Hillingdon Hospital
University Hospital Lewisham
Whittington Hospital
Hemel Hempstead General Hospital
Watford General Hospital
West Middlesex University Hospital
Whipps Cross Hospital
Worthing Hospital
The Royal London Hospital
Great Ormond Street Hospital
The Royal Marsden Hospital
Middlesex Hospital (now closed)

Appendix 2. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.06.003.

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