children. It will take time to implement these suggestions nationwide, but the direction of travel and the needs are clear—improved and measured quality of care, improved training and improved systems. Regarding the care of children, many emergency care facilities focus on the care of children under age 5 years. The needs of older children and young adults also need consideration but are often forgotten, as fewer sites focus on 24 h paediatric services, it is vital that appropriate networks of care for children and young people with emergencies are developed and that paediatric services are represented on all urgent care networks.

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Low-risk febrile neutropenia

Treating low-risk febrile neutropenia: Jenny's story

R Phillips, R Skinner, J C Chisholm

Some paediatric patients with cancer can be treated with antibiotic regimens of reduced intensity and duration

Jenny is an imaginary 4-year-old girl on maintenance treatment for acute lymphoblastic leukaemia. She gets a cold and a temperature of 38.3°C, and her parents take her to the local hospital. Examination shows no apparent cause of infection, but her temperature remains increased and her neutrophil count is low at $0.7 \times 10^9/l$. Today, in the UK, the manner in which local hospitals treat such an episode varies considerably. After appropriate investigation, including blood and urine cultures, Jenny may be sent home with a recommendation to return if she becomes unwell, or if her temperature continues over the next few days, she may be started on oral antibiotics as an inpatient, with discharge after 48 h, or she may be started on intravenous antibiotics with a view to discharge on oral antibiotics at 48 h, or she may stay in hospital on intravenous antibiotics for a minimum of 5 days. Compare this with how Jenny is treated with chemotherapy for her acute lymphoblastic leukaemia, receiving the same national treatment regimen regardless of where she lives. For most patients, the difference between approaches to treatment of febrile neutropenia is never noticed as children are treated consistently at their individual hospitals, but imagine the potential for confusion or uncertainty if Jenny becomes unwell when she goes to visit her Aunt Minnie in a different part of the country.

The striking variation across the UK in the treatment of febrile neutropenia exemplifies the lack of consistency between paediatric oncology centres in their protocols for supportive care. Some centres are already using strategies to identify episodes of febrile neutropenia where the risk of life-threatening complications is low (acute medical deterioration, admission to the intensive care unit or death from sepsis), and are actively reducing the duration or intensity of antibiotics given during such episodes. Several studies have shown that this can be accomplished effectively and safely in selected low-risk episodes, in both specialist and non-specialist units.¹ Other centres continue to treat all episodes of febrile neutropenia with the standard approach of the past 30 years, using inpatient broad-spectrum intravenous antibiotics until the resolution of fever, without attempting risk stratification. It is interesting to contemplate the emergence of such variability. No large-scale, cooperative, randomised trials have been conducted for paediatric oncology supportive care, unlike the therapeutic studies on childhood cancer that are the envy of other specialities. In Europe, particularly in adult practice, the European Organisation for the Research and Treatment of Cancer has conducted studies on antibiotic treatment for febrile neutropenia that have influenced practice,²

but there are no cooperative trials focusing specifically on children. Local microbiological differences certainly exist and explain some of the local variation in antibiotic policy for febrile neutropenia, but do not account for other fundamental differences such as the degree of neutropenia (eg $<1.0 \times 10^9/l$ in some units, $<0.5 \times 10^9/l$ in others) chosen as the threshold for starting empirical treatment with antibiotics.

Intensive management approaches have reduced death rates to 1% and admission rates for paediatric intensive care units to $<5\%$ in paediatric febrile neutropenia.¹ About 50% of episodes of paediatric febrile neutropenia have no documented clinical or microbiological site of infection.³ Low-risk febrile neutropenia episodes are those in which it is very unlikely that there will be a life-threatening complication and are usually those without an identifiable, clinically relevant infection. For these episodes, it may be appropriate to reduce the duration or intensity of the antibiotics. Large-scale adult studies have produced detailed scoring systems to identify episodes of low-risk febrile neutropenia within the first 24 h of initial presentation.^{4–5} Even so, these scoring systems are not perfect, and serious complications or even death from infection are seen occasionally in low-risk episodes. Paediatric definitions are not as clear: the data that exist seek to define the risk of bacteraemia or invasive bacterial infection (as a surrogate for medical complications), and come from studies in single centres or a small group of centres. Only three sets of data have sought to validate a risk-prediction system.^{6–8} These define similar themes: episodes with a low risk of bacteraemia or invasive bacterial infection are those in which children are outpatients at the onset of the febrile neutropenia episode, are clinically well and show evidence of, or are predicted to have, impending bone marrow recovery.

Despite the lack of a single, validated risk-prediction system for paediatric

febrile neutropenia, many studies have compared differing approaches to treatment in febrile neutropenia episodes identified as low risk by local criteria. Useful approaches to reduced-intensity treatment include early discharge on ambulatory intravenous treatment, step-down treatment (starting with intravenous antibiotics and moving to oral treatment after a period of 8–48 h), or oral antibiotics from the outset of the episode, given in the hospital or as an outpatient. It is likely that many children with low-risk febrile neutropenia do not need any antibiotics at all, but at the moment we cannot adequately identify these patients early in the course of the episode. In the future, strategies such as the use of highly specific markers of inflammatory response might enable us to identify such episodes so that we can avoid antibiotics altogether in carefully selected low-risk episodes.⁹

Early discharge on ambulatory intravenous treatment has been shown in a small randomised trial to be as effective as continued inpatient treatment.¹⁰ However, other trials have shown that a step-down to early discharge on oral antibiotics can produce similar results,^{11–12} which is a more widely used approach in children. Step-down after 48 h of treatment as an inpatient was shown to be practical in the UK both in specialist paediatric oncology centres and local shared-care units,¹³ and such a strategy is potentially applicable to about one-quarter of febrile neutropenia episodes.¹⁴ Specialist centres with an interest in febrile neutropenia have been able to maximise the utility of the step-down approach by giving a single dose of intravenous antibiotics before discharge on oral antibiotics after a brief period of observation.^{8–15}

Treatment with oral antibiotics from the onset of febrile neutropenia has been viewed with great caution in children. Studies on an adult population with cancer have shown equivalence to intravenous treatment in selected low-risk patients with febrile neutropenia,¹⁶ but there are few data regarding its use in the paediatric population. Those that exist are encouraging^{17–19} but many clinicians still have considerable discomfort with this approach, and equivalence to other strategies has not been proved in a well-designed randomised controlled trial. The safety of oral treatment depends on good risk stratification and, until we can reliably identify patients without bacterial infection, on the use of well-absorbed oral broad-spectrum antibiotics, such as ciprofloxacin with coamoxiclav which will cover the full range of potential infections including Gram-negative organisms.

The Supportive Care Group of the United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum is in the process of building a framework guideline

that seeks to unify the management of low-risk febrile neutropenia across the UK, with an emphasis on the step-down approach. The widespread implementation of this guideline will be an important step in advancing the supportive care of children with malignant disease, with an aim similar to that of many current therapeutic studies seeking a reduction in treatment-related morbidity (eg the International Childhood Liver Tumour Strategy Group SIOPEL 3 study comparing single-agent cisplatin with the established cisplatin/doxorubicin strategy for hepatoblastoma, or the United Kingdom Acute Lymphoblastic Leukaemia 2003 trial randomising patients with acute lymphoblastic leukaemia who have low levels of minimal residual disease to fewer blocks of intensive chemotherapy). The adoption of this treatment framework will hopefully generate new opportunities in the future to resolve issues, such as whether an oral antibiotic strategy is as safe as a step-down approach, with comparison of health-care costs and acceptability to families, and whether the lowest risk group can be treated successfully in the outpatient setting. These questions are currently the subject of trials in adult practice, but the difference between the age-defined populations is large enough to demand separate studies in children and young people.³

In summary, it is now possible to define a group of paediatric patients with cancer who can be treated with antibiotic doses of reduced intensity and duration. We have the chance to standardise the approach to the management of low-risk febrile neutropenia on the basis of current evidence (taking into account local microbiological environments). Further, by developing good clinical trials based on this approach, we can endeavour to advance the supportive care of children with cancer as conscientiously as we have with clinical trials on cytotoxic treatment. In time, if Jenny is unwell when she visits Aunt Minnie, she will be treated with the same consistency in supportive care as she already receives in chemotherapy.

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