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| **Innes, H. E., Smith, D. B., O'Reilly, S. M., Clark, P. I., Kelly, V., & Marshall, E. (2003). Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. British Journal of Cancer, 89, 43-49.** |
| **Country:**<br><br>United Kingdom |
| **Design:**<br><br>Randomised Controlled Trial |
| **Population:**<br><br>126 episodes of low risk neutropenia in 102 patients between February 1997 and August |

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| 2000 |
| **Inclusion criteria:**<br><br>Age ≥ 18<br><br>Neutropenia (defined as (ANC) ≤ 0.5 x $10^9$ $1^{-1}$, or (ANC) ≤ 1 x $10^9$ $1^{-1}$ but anticipated to fall to (ANC) ≤ 0.5 x $10^9$ $1^{-1}$ within 24 hours of entry into the study)<br><br>Fever (defined as a temperature ≥38°C on two oral measurements 4 hours apart within a 24 h period, one of which could have been measured by the patient prior to admission, or ≥38.5°C on one occasion)<br><br>Anticipated duration of neutropenia < 7 days<br><br>Haemodynamically stable<br><br>No signs or symptoms that required intravenous fluid support<br><br>Adequate renal function<br><br>Ability to maintain satisfactory oral intake<br><br>Living with responsible adult prepared to act as a carer if eligible for early discharge<br><br>Either patient or carer required to be able to read a thermometer<br><br>Written informed consent |
| **Exclusion criteria:**<br><br>Autologous bone marrow or peripheral blood stem-cell transplantation<br><br>Antibacterial medication within 7 days of enrolment.<br><br>Use of CSFs and cytokines<br><br>Any coexisting medical condition that would require in-patient treatment or monitoring<br><br>Clinically documented infection in the opinion of the investigator, likely to require targeted or prolonged duration of antibiotic therapy (e.g. cellulitis, abscess, pneumonia, CVC tunnel infection)<br><br>Inability to tolerate oral medication<br><br>Known allergy to study drugs |

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| History of poor compliance |
| **Interventions:**<br><br>Oral regimen: Ciprofloxacin 750 mg every 12 h plus amoxicillin–clavulanate (amoxicillin 500 mgþclavulanate 175 mg) every 8 h for a total of 5 days. Participants were eligible for discharge following 24 h of hospitalisation if clinically stable, symptomatically improved, and willing. Patients supplied with daily diary to record temperature at 6-hourly intervals and any associated symptoms, and telephone contact was maintained. Those randomised to the oral arm who were not discharged after the 24 h assessment were reassessed daily including their eligibility for discharge.<br><br>Intravenous regimen: Gentamicin 80 mg every 8 h and dose adjusted according to therapeutic levels plus tazocin (piperacillin 4 gþtazobactam 500 mg; Lederle, Maidenhead, UK) every 8 h until hospital discharge.<br><br>*** BOTH GROUPS WERE ELIGIBLE FOR DISCHARGE IRRESPECTIVE OF ANC*** |
| **Outcomes:**<br><br>Success (defined by the EORTC guidelines)<br><br>Lysis of fever<br><br>Recurrence within 7 days<br><br>Frequency of serious medical complications<br><br>Frequency of deaths<br><br>Duration of hospital admission<br><br>Frequency of readmission<br><br>Toxicity |
| **Results:**<br><br>Success (according to EORTC guidelines)<br><br>Oral: 90% of episodes treated successfully without antibiotic modification<br>IV: 84.8% of episodes successfully without antibiotic modification<br><br>Death<br><br>Oral: 0<br>IV: 1 |

Significant clinical deterioration

Oral: 1 ( (during initial 24 hours of inpatient monitoring)
IV: 0

Length of hospital stay

Oral: 2 days (range 1–16 days)
IV: 4 days (range 2–8)

Readmission to hospital
Oral: 5 (13.2%)

Toxicity
Oral: 1 episode CTC grade 3; 14 patients CTC grade 1-2 diarrhoea; 5 patients CTC grade 1-2 nausea/vomiting
IV: No episodes of toxicity CTC grade > 1

**General comments:**

This was a well conducted RCT. The sample size was fairly small, but a power calculation was reported. The definition of 'low-risk' was based on the definition proposed by Talcott et al (1988), but given the intention of early hospital discharge and the high incidence of complications and readmissions in Talcott's initial pilot study, the definition was extended to exclude central venous catheter infections, pneumonia and cellulitis and an expected duration of neutropenia of over 7 days. Eligible patients were randomly assigned to study groups by means of consecutively drawn sealed envelopes. Patients could be entered more than once following subsequent episodes of febrile neutropenia. The study was conducted before development of the MASCC. The authors concluded that oral antibiotics in conjunction with early hospital discharge for patients who remain stable after a 24 h period of in-patient monitoring offers a feasible and cost-effective alternative to conventional management of low-risk neutropenic fever.

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| **Santolaya, M. E., Alvarez, A. M., Aviles, C. L., Becker, A., Cofre, J., Cumsille, M. A. et al. (2004). Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. Journal of Clinical Oncology, 22, 3784-3789.** |
| **Country:**<br><br>Chile |
| **Design:**<br><br>Randomised Controlled Trial |

**Population:**

390 episodes of febrile neutropenia at six hospitals in Santiago, Chile between June 2000 and February 2003.

**Inclusion criteria:**

Age ≤ 18

Fever (one axillary recording of 38.5°C or greater or two recordings of 38°C or greater separated by at least 1 hour)

Severe neutropenia (ANC < 500/µL)

**Interventions:**

Children at low risk of Invasive Bacterial Infection (IBI) were admitted to the hospital. Empirical IV antimicrobial treatment was administered (ceftriaxone 100 mg/kg/d every 24 hours, and IV teicoplanin 20 mg/kg/d every 12 hours for the first day followed by 10 mg/kg/d every 24 hours). They were re-evaluated after 24 to 36 hours to determine whether they continued in the low-risk category. After completing a minimum of 3 days of IV therapy, those who met criteria for low risk switched therapy to oral cefuroxime axetil, 50 mg/kg/d every 12 hours and randomly assigned to receive ambulatory or hospital management.

**Outcomes:**

Unfavorable outcome defined by: (1) hemodynamic instability not attributable to volume loss; (2) axillary temperature more than 38°C in two or more daily recordings after day 4; (3) increase in temperature after a 48-hour afebrile period persisting for at least 24 hours; (4) an ascending CRP curve or a nondescending curve over normal limits (a value > 40 mg/L and < 30% decrease from a previous recording) after day 3 persisting for at least 2 consecutive days; (5) isolation of a bacterial pathogen from a significant sample obtained on day 3; and (6) death occurring during the febrile episode attributable to infection.

**Results:**

161 (41%) of 390 febrile neutropenic episodes were classified as low risk

149 were randomly assigned to ambulatory (n = 78) or hospital-based (n = 71) treatment.

<u>Favourable outcome</u>

Ambulatory-treated children: 74/78 (95%)

Hospital-treated children: 67/71 (94%)

Mortality

Ambulatory-treated children: 0/78 (0%)

Hospital-treated children: 1/71 (1%)

**General comments:**

Work by the authors from 1996 to 1997, aimed to identify clinical and laboratory variables present at the time of first consultation that could help identify children at high or low risk of an IBI. The following five independent risk variables (ranked by order of significance) were identified: serum C-reactive protein (CRP) levels of 90 mg/L or greater, presence of hypotension, relapse of leukemia as cancer type, platelet count of 50,000/µL or less, and recent (≤ 7 days) chemotherapy. IBI occurred in 2%, 17%, 48%, 75%, and 100% of episodes presenting with none, one, two, three, or four or more risk factors, respectively. During 1999 to 2000, the model was prospectively validated. Sensitivity, specificity, and positive and negative predictive values for this model were 92%, 76%, 82%, and 90%, respectively. This study aimed to evaluate the hypothesis that children at low risk for IBI can be treated as outpatients and have a comparable outcome to children treated in hospital. It is unclear how patients were randomised. A power calculation is presented. The authors concluded that for children with febrile neutropenia at low risk for IBI, ambulatory management is safe and significantly cost saving compared with standard hospitalised therapy.

| **Lau, R. C., Doyle, J. J., Freedman, M. H., King, S. M., & Richardson, S. E. (1994). Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. Pediatric Hematology & Oncology, 11, 417-421.** |
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| **Country:**<br><br>Canada |
| **Design:**<br><br>Open un-randomised comparative feasibility study |
| **Population:**<br><br>23 episodes of febrile neutropenia in 21 patients admitted to hospital between October |

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| 1990 and July 1991 |
| **Inclusion criteria:**<br><br>Fever (no definition)<br><br>Neutropenia after chemotherapy (no definition) |
| **Exclusion criteria:**<br><br>Fever longer than 48 hours after receiving IV antibiotics<br><br>Blood culture positive<br><br>Sepsis clinically suspected |
| **Interventions:**<br><br>All patients were initially treated with 72 hours of intravenous antibiotic therapy (tiracillin 200 mg/kg/day every 6 hours) and gentamicin (7.5mg/kg/day every 8 hours).<br><br>After 72 hours, IV antibiotics changed to oral antibiotics if all following criteria met: negative blood cultures, temperature 38ºC or lower for 24 hours, absolute neutrophil count (ANC) less than 0.5 X $10_9$/L, absence clinical sepsis.<br><br>Oral antibiotics were cefixime (8mg/kg/day; maximum 400mg) as a single dose and cloxacillin (100mg/kg/day in 4 divided doses; maximum, 1g per dose)<br><br>First 12 patients monitored as inpatients<br><br>Remaining 11 patients were discharged and followed as outpatients: Asked to record temperature daily and have a complete blood count done every 3 days. |
| **Outcomes:**<br><br>Fever recurrence<br><br>Clinical deterioration |
| **Results:**<br><br>Fever recurred in 3 patients (13%). IV was reinstated in 2 cases, and oral antibiotics continued in the third.<br><br>No patients showed clinical deterioration |
| **General comments:**<br><br>This was a very small scale open feasibility study of paediatric cancer patients |

presenting with febrile neutropenia. They were treated with intravenous and then oral antibiotics if meeting criteria indicating low risk. The first 12 patients were treated as inpatients and the remaining 11 as outpatients. It is unclear why these patients were not randomly assigned to groups. The results were very badly reported. Fever recurred in three patients, but it is unclear whether these were in the inpatient or outpatient group. Indeed, it is unclear how the two groups differed in terms of any outcome. The authors concluded that the approach could be used safely in a carefully selected group of patients.

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| **Bash, R. O., Katz, J. A., Cash, J. V., & Buchanan, G. R. (1994). Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. Cancer, 74, 189-196.** |
| **Country:**<br><br>USA |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>131 episodes of febrile neutropenia in 74 patients admitted to a children's medical centre between November 1989 and July 1990 |
| **Inclusion criteria:**<br><br>Fever (single temperature ≥ 38.5°C or serial measurements of ≥ 38°C for more than 6 hours)<br><br>Neutropenia (defined as ANC ≤ 500/$mm^3$)<br><br>Parental informed consent |
| **Interventions:**<br><br>Intravenous ceftazidime (50mg/kg/dose, maximum dose 2.0g) administered to all patients and repeated every 8 hours. Additional antibiotics were administered for specific indications at the clinicians discretion<br><br>Patients were eligible for discontinuation of antibiotics and early discharge if they met the following criteria:<br><br>1. Afebrile for at least 24 hours |

2. Appeared clinically well
3. Negative blood cultures for at least 48 hours
4. Control (improvement or resolution) of local infection
5. Evidence of bone marrow recovery for at least 1 day (increase in leukocyte, APC, ANC, and/or platelet count)

If localised infection had not fully resolved: discharged with oral antibiotics.

Discharged patients maintained daily telephone contact and were monitored as outpatients every 2-3 days as outpatients as long as they remained neutropenic.

**Outcomes:**

% patients discharged early

Hospital readmission

Mortality

**Results:**

82/131 (63%) episodes were eligible for early discontinuation of IV antibiotics

78/131 (58%) were discharged early

Hospital readmission

7 (9%) patients were re-admitted (although these were retrospectively said not to meet the full criteria for early discharge)

Mortality

0 (0%) died

**General comments:**

This was a prospective case series with a relatively small sample size of 74 patients. Criteria for early discharge were presented. It is unclear however what specifically is meant by the criterion “clinically well”. It is reported that additional antibiotics were given alongside empiric IV antibiotics, but no details are given as to what these were, or how many patients received them. 8/78 patients discharged early were said to be protocol violations on the basis that there had been no sustained rise in leukocyte, ANC, APC, or platelet count. 6/8 (75%) were readmitted. The results reported in the abstract ignore these readmissions, reporting only that none of the 70 they retrospectively deemed to meet criteria were re-hospitalised. The authors concluded that low risk children with cancer who are hospitalized and treated for fever and neutropenia but

appear clinically well may have intravenous antibiotics discontinued and be discharged safely irrespective of the ANC, as long as their granulocyte count is rising.

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| **Cherif, H., Johansson, E., Bjorkholm, M., & Kalin, M. (2006). The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. Haematologica, 91, 215-222.** |
| **Country:**<br><br>Sweden |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>191 adult patients, who developed 279 episodes of febrile neutropenia (participants could be re-entered into the study for a second time (but not a third) providing neutrophile count had returned to normal between episodes).<br><br>Represented all adult patients admitted to a medical unit between November 2003 and April 2005 for the treatment of fever and neutropenia associated with chemotherapy. |
| **Inclusion criteria:**<br><br>Fever (defined by a temperature of ≥38°C on two occasions at least 4 hours apart during a 24-hour period or ≥38.5°C on a single occasion)<br><br>Neutropenia (defined as ANC ≤ 0.5 x $10^9$/L)<br><br>Written informed consent |
| **Interventions:**<br><br>All participants were hospitalised to receive IV antibiotics “in accordance with local and international recommendations”.<br><br>Low risk patients according to MASCC criteria (score ≥ 21), who had not developed clinical complications, were transferred to oral antibiotics 24 hours after fever subsided. The first dose was administered in hospital, and if no acute complications arose, they were subsequently monitored as outpatients. Oral antibiotic treatment was continued for 5 days. |

**Outcomes:**

Sensitivity, specificity and positive predictive value of MASCC

Mortality

Hospital re-admission

**Results:**

Low risk according to MASCC: 105 (38%) episodes occurring in 81 patients

High risk according to MASCC: 174 (62%) episodes occurring in 132 patients

MASCC specificity: 87%

MASCC sensitivity: 58%

MASCC positive predictive value: 84%

36% of low-risk group were ineligible for oral antibiotics

Of the 67 patients who received oral antibiotics and early discharge, 64 (95%) remained afebrile, 3 required re-admission, and there was no mortality.

**General comments:**

This was a reasonably well conducted prospective case series including all adult patients admitted to a medical-centre between November 2003 and April 2005 for the treatment of fever and neutropenia associated with chemotherapy. The methodology allowed collection of data from the same participant up to two times, which somewhat compromises the data-set overall. It is unclear why this was allowed, whilst excluding third cases. The MASCC was developed using a single episode per patient, and its validity for second episodes is currently known. Including multiple episodes is however the case in the vast majority of studies considered here. No demographic information was included (e.g. age, gender, ethnicity), which might have been useful in providing context to the results. 36% of the low-risk group were ineligible for oral antibiotic. The authors concluded that the MASCC risk-index was a valuable tool for identifying febrile neutropenic patients at low risk for complications and that oral antibiotic treatment following discharge from the hospital 24 hours after defervescence offered a safe and cost-effective alternative to the conventional management of carefully selected low-risk patients.

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| **Girmenia, C., Russo, E., Carmosino, I., Breccia, M., Dragoni, F., Latagliata, R. et al. (2007). Early hospital discharge with oral antimicrobial therapy in patients with hematologic malignancies and low-risk febrile neutropenia. Annals of Hematology, 86, 263-270.** |
| **Country:**<br><br>Italy |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>100 episodes of febrile neutropenia in 87 consecutive patients hospitalised between March 2001 and August 2002 |
| **Inclusion criteria:**<br><br>Age ≥ 16<br><br>Haematological malignancy<br><br>Neutropenia (defined as ANC < 500 cells /µl of blood)<br><br>Fever (defined as temperature ≥ 38.5ºC on one occasion, or ≥ 38 ºC for more than an hour) |
| **Interventions:**<br><br>All patients were treated with empiric intravenous ceftriaxone (2g/24h) plus amikacin (20 mg/kg/24h) within an hour of arrival at EU. The therapeutic plan was to continue antibiotics for 6 consecutive afebrile days had passed, or until microbiological and/or clinical evidence of infection had disappeared.<br><br>The Multinational Association of Supportive Care in Cancer (MASCC) criteria were used to categorise patients as high risk (score < 21) or low risk (score ≥ 21). This classification dictated subsequent management.<br><br><u>High risk patients:</u> managed in hospital for entire course of antibiotic treatment regardless of neutropenia recovery and response to treatment.<br><br><u>Low risk patients:</u> discharged from hospital early if free from fever for 48 hours, in a good general condition and not receiving supportive treatment requiring hospitalisation. |
| **Outcomes:** |

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| Length of hospital stay<br><br>Fever recurrence<br><br>Mortality |
| **Results:**<br><br>Of 90 low-risk episodes, 69 (76.7%) cases were discharged early after a median of 4 days, and continued home therapy with oral cefixime (78%) or other antibiotics<br><br>5 (7.2%) of those discharged early had fever recurrence<br><br>21 low-risk patients were not discharged early due to worsening conditions (three deaths), need of multiple daily dose therapy, or discharge refusal<br><br>0 (0%) early discharge patients died |
| **General comments:**<br><br>Consecutive cases were prospectively evaluated. The sample size was fairly small. The authors concluded that the MASCC risk-index was a useful aid in the identification of high-risk febrile neutropenia needing their entire treatment in hospital. They also noted that hospitalisation for the first few days of fever was required on the basis that ¼ of low-risk patients required prolonged hospitalisation, and three died of non-infectious causes. |

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| **Klastersky, J., Paesmans, M., Georgala, A., Muanza, F., Plehiers, B., Dubreucq, L. et al. (2006) Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. Journal of Clinical Oncology, 24 (25) 4129-4134** |
| **Country:**<br><br>Belgium |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>383 febrile neutropenic episodes with low risk of complications who were treated with chemotherapy from January 1999 to November 2003 |

**Inclusion criteria:**

Age ≥ 16

Neutropenia (defined by ANC ≤ $0.5x10^9$/L)

Fever (defined by temperature ≥38.5ºC on one occasion, or ≥38 ºC twice during a 12 hour interval)

Able to swallow

Free of contraindications for oral drugs

Informed consent

Low risk was defined as MASCC score ≥ 21

**Exclusion criteria:**

History of allergy to penicillin or quinolones

**Interventions:**

Oral antibiotics (ciprofloxacin and amoxicillin-clavulanate); discharged if they clinically stable or improving after an initial observation period.

**Outcomes:**

Early discharge

Hospital readmission

Clinical complications

**Results:**

178 of 383 first febrile neutropenic episodes predicted at low risk of complication (score of 21 or less on the MASCC) were treated orally. These cases constituted the analysis.

<u>Early discharge</u>

79 (44%) were discharged early (median time to discharge of 26 hours);

<u>Clinical complications</u>

0 (0%) clinical complications occurred

<u>Hospital readmission</u>

3 (4%) patients had to be readmitted to hospital

Success rate of 96% (95% CI, 92% to 100%).

**General comments:**

All febrile neutropenic patients between January 1999 and November 2003 were screened and assessed on the MASCC. The majority of participants (81%) were female. A power calculation was reported. A major limitation of the study was the fact that most patients with hematologic tumours were excluded. The institution routinely provided antibacterial prophylaxis for these individuals, and this was an exclusion criterion for oral antibiotic administration. Exclusion of these patients acted as an additional filter independent of the tool under investigation. The authors concluded that oral therapy followed by early discharge was feasible in a small but significant proportion of low risk patients (although this conclusion cannot be generalised to individuals with hematologic tumours)

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| **Tomiak, A. T., Yau, J. C., Huan, S. D., Cripps, M. C., Goel, R., Perrault, D. J. et al. (1994). Duration of intravenous antibiotics for patients with neutropenic fever. *Annals of Oncology, 5,* 441-445.** |
| **Country:**<br><br>Canada |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>134 episodes of febrile neutropenia in adult neutropenic admissions to a medical oncology ward between September 1991 and March 1993 |
| **Inclusion criteria:**<br><br>Fever (defined as single temperature ≥ 38.5°C, or two or more recordings ≥ 38.0°C within hours).<br><br>Neutropenia (defined as ANC less than 0.5 x $10^9$/L) |
| **Exclusion criteria:**<br><br>Developed febrile neutropenia while in hospital |
| **Interventions:**<br><br>A policy of early discontinuation of intravenous antibiotics was adopted in April 1992. This consisted of discontinuation of intravenous antibiotics in culture negative patients who remained afebrile and clinically stable for 48 hours, regardless of their absolute neutrophil counts. (Clinically stable was defined as hemodynamically stable with no |

clinical signs of worsening infection and able to maintain adequate oral intake.)

Patients were started on oral antibiotics and discharged at the discretion of the attending physician. Patients were generally monitored for an additional 24-48 hours prior to discharge to ensure that they remained afebrile and clinically stable; the length of observation varied between attending physicians and their level of comfort with early discharge.

Oral antibiotics were generally continued for a total of 7-10 days.

In order to observe the effect of this policy the study period was divided into three intervals with equal number of admissions in each interval.

Group 1: patients managed prior to the initiation of policy. Antibiotics were continued in culture negative patients until resolution of both fever and neutropenia or at the discretion of attending physicians.

Group 2: patients admitted after starting the policy of early discontinuation of intravenous antibiotics.

Group 3: included to monitor if the policy was still implemented.

**Outcomes:**

Hospital readmission

Reinstitution of IV antibiotics

Mortality

Median duration of IV antibiotic

Median duration of hospital stay

**Results:**

<u>Early discharge</u>

37/134 (28 %)

<u>Hospital readmission</u>

2/37 (5%)

<u>Reinstitution of IV antibiotics</u>

0 (0%)

Mortality

1/37 (3%)

Median duration of IV antibiotic

Group 1: 7 days

Group 2: 5 days

Group 3: 4 days

Median duration of hospital stay

Group 1: 10 days

Group 2: 7 days

Group 3: 6 days

**General comments:**

This was a retrospective review of patient records. A policy of early discharge had been implemented, and the authors aimed to compare patient data before implementation, after implementation and at a later date. Patients in Group 1 were treated up to two years before Group 3. It is unclear whether there were any other changes to treatment regimens during this time. Patients were treated at different times of the year (groups 1 and 3 over the summer, and group 2 over the winter). It appears that each episode of FN represented an individual patient. The authors do not state that subsequent episodes were excluded, but it seems unlikely that none of these patients developed FN for a second time. 27% of patients were discharged early, but it is unclear whether these patients belonged to group 1, 2, or 3.

| **Lehrnbecher,T.; Stanescu,A.; Kuhl,J. (2002) Short courses of intravenous empirical antibiotic treatment in selected febrile neutropenic children with cancer. Infection, 30 (1), 17-21** |
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| **Country:**<br><br>Germany |
| **Design:** |

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| Retrospective consecutive case series |
| **Population:**<br><br>106 episodes of chemotherapy induced neutropenia and fever in 56 children admitted to an oncology ward between January 1994 and June 1996 |
| **Inclusion criteria:**<br><br>Aged < 18<br><br>Neutropenia (defined as less than 500 neutrophils/ml, or patients who had recently received chemotherapy and had evidence of rapidly dropping neutrophil counts with an ANC of less than 500/µl within 72 hours were also included).<br><br>Fever (defined as temperature ≥ 38.5ºC on one occasion, or two measurements of ≥ 38 ºC within 4 hours) |
| **Exclusion criteria:**<br><br>Antibiotics within 72 hours of admission (apart from trimethoprim sulfamethoxazole prophylaxis) |
| **Interventions:**<br><br>Until April 1995: initial empirical antibiotic therapy – ceftazidime 150mg/kg/d in three divided doses and teicoplanin 10mg/kg/d twice the first day and then once daily<br><br>From May 1995: initial empirical antibiotic therapy – imipenem monotherapy 50mg/kg/d divided in four doses. Teicoplanin 10mg/hg/d twice the first day and then once daily was added if fever persisted longer than 72h and neutrophil recovery was not evident<br><br>In both treatment regimens initial antibiotic therapy was continued in patients with FUO who were in good clinical condition and ANC was rising or there was indication of bone marrow recovery. Antibiotic therapy was discontinued and patients were discharged from hospital when they met the following criteria: good clinical condition, negative blood culture results and no infectious focus, absence of fever for at least 24 h without antipyretics and antibiotic treatment for a minimum of 72 h. An ANC greater than 500/µl or evidence of bone marrow recovery were not a precondition for the discontinuation of antibiotic therapy. Parents monitored temperature three times daily<br><br>In patients with microbiologically or clinically documented infection, antibiotic therapy was continued for at least 7 days. Empirical antifungal therapy was started in neutropenic patients with persistent or recrudescent fever that occurred after 5 days of broad-spectrum antibiotics. Standard regimens were modified if the patient had microbiological or clinical evidence of an infection that was not |

adequately treated.

**Outcomes:**

Mortality

Reoccurrence of fever

Rehospitalisation

**Results:**

24 out of the 41 neutropenic FUO treated with empirical monotherapy with imipenem, fever resolved within the first 72 h and patients were discharged after 24 h of defervescence regardless of ANC

Reoccurrence of fever

0 (0%) showed recurrent fever

Rehospitalisation

0 (0%) had to be rehospitalized

Mortality

0 (0%) died

**General comments:**

This was a retrospective analysis of patients who received a short course of IV antibiotic therapy, which allowed early hospital discharge and discontinuation of antibiotic therapy regardless of ANC or evidence of bone marrow recovery, as long as patients were afebrile for at least 24 hours and had been treated for a minimum of 72 hours. Initial empirical antibiotic therapy was changed during the period of time the study reviewed. Only 24 patients were discharged early, so results related to this sub-group is based on a very small sample size. The authors conclude that discontinuation of intravenous antibiotics regardless of ANC or evidence of bone marrow recovery seems safe and effective in pediatric cancer patients with FUO when children are afebrile for at least 24 h and are treated for a minimum of 72 h.

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| **Dommett, R., Geary, J., Freeman, S., Hartley, J., Sharland, M., Davidson, A. et al. (2009). Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. European Journal of Cancer, 45, 2843-2849.** |
| **Country:**<br><br>United Kingdom |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005 |
| **Inclusion criteria:**<br><br>Age < 18<br><br>Neutropenia (defined as ANC < $1.0x10^9$/L)<br><br>Fever (single temperature of ≥ 38.5°C or sustained temperature of >38°C over 4 hours) |
| **Interventions:**<br><br>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).<br><br>A checklist of risk factors was administered at the start of each FN episode and 48 hours later. Episodes were designated low risk if no risk factors were identified at either time point. All other episodes were designated standard risk. Fever at 48 hours did not exclude from the low risk strategy.<br><br>The checklist was as follows: Age<1 year, 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, peri-rectal or other soft tissue abscess, rigors, irritability/meningism, organ failure, acute lymphoblastic leukaemia at diagnosis/relapse <28 d, acute lymphoblastic leukaemia not in remission >28 d acute myeloid leukaemia, |

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| infant acute lymphoblastic leukaemia, intensive B-NHL protocols, haemopoietic stem cell transplant, sequential high dose chemotherapy with PBSC rescue, intensive care admission during last FN episode, non adherence (social concerns or patient), inability to tolerate oral antibiotics, positive blood culture result at 48 h, ANC < 0.1 · 109/L at 48 h, child not clinically well at 48 h (clinician judgement).<br><br>Low risk episodes: discharged at 48 h taking oral co-amoxiclav until 48 h after resolution of fever (<37.5ºC). 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. Patients remaining febrile at 96 hours were readmitted to hospital for intravenous antibiotics and amphotericin preparation. Children could also be readmitted at other times if concerns were raised. |
| **Outcomes:**<br><br>Hospital readmission<br><br>Intensive care admission<br><br>Mortality |
| **Results:**<br><br>In 40% of episodes no clinical or microbiological focus could be found.<br><br>At 48 hours, 212 (27%) of episodes were classified as low risk<br><br>143 (19%) were managed on the low risk protocol.<br><br>Hospital readmission<br><br>8 /143 (5.6%) were re-admitted to hospital<br><br>Intensive care admission<br><br>There were no intensive care admissions<br><br>Mortality<br><br>There were no deaths. |

**General comments:**

This was a well conducted, reasonably large scale prospective study/audit of practice at four non-specialist paediatric oncology centres. Using a step-down strategy only 19% of patients were managed using the Low Risk protocol, despite 28% being eligible. The most common reason for failure to manage according to the low risk strategy was 'clinical decision'. The exact reasons for these decisions were not elaborated upon, but the authors suggest that there may have been a wariness to adopt the strategy, which may be remedied as data on the safety of the approach is disseminated. The authors concluded that rapid step down to oral antibiotics was a feasible and safe management strategy for LR FN in the shared care setting in England.

| **Tordocilla, C. J., Campbell, B. M., Joannon, S. P., & Rodriguez, R. N. (1994) Neutropenia and fever. Revista Chilena de Pediatria, 65 (5) 260-263** |
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| **Country:**<br><br>Chile |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>84 episodes of FN in 50 patients admitted to a children's hospital in Santiago, Chile, between April 1992 and July 1993. |
| **Inclusion criteria:**<br><br>Age < 18<br><br>Neutropenia (ANC ≤ 500 cells per cubic millimetre)<br><br>Fever (temperature ≥ 39°C on a single occasion, or ≥ 38°C on separate occasions within 4 hours) |
| **Interventions:**<br><br>Patients were discharged early if they became afebrile, appeared well, had negative blood cultures, and had normal chest x-ray, in spite of ANC. |
| **Outcomes:** |

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| Length of hospital stay<br><br>Hospital readmission<br><br>Mortality |
| **Results:**<br><br>30 episodes of fever and neutropenia (35.7%) were discharged early<br><br><u>Length of hospital stay</u><br><br>Mean 5.1 days of hospitalization<br><br><u>Hospital readmission</u><br><br>0 (0%) patients required readmission to hospital within the next seven days<br><br><u>Mortality</u><br><br>0 (0%) patients died |
| **General comments:**<br><br>This paper was written in Spanish. Data was extracted from the English language abstract. The authors concluded that some low risk patients with cancer and febrile neutropenia could be discharged early in spite of neutropenia. |

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| **Aquino, V. M., Buchanan, G. R., Tkaczewski, I., & Mustafa, M. M. (1997) Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. Medical and Pediatric Oncology, 28 (3), 191-195** |
| **Country:**<br><br>USA |
| **Design:**<br><br>Retrospective case series |
| **Population:**<br><br>580 consecutive episodes of chemotherapy induced febrile neutropenia in 253 children |

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| and adolescents with cancer between June 1992 and May 1995 |
| **Inclusion criteria:**<br><br>Neutropenia (defined as ANC<500 cells/$mm^3$)<br><br>Fever (temperature of >38.5°C on a single occasion, or 2 measurements of 38.0°C in a 24 hour period) |
| **Exclusion criteria:**<br><br>Bone marrow transplantation |
| **Interventions:**<br><br>Most patients received empiric ceftazidime as initial antimicrobial therapy. Patients were treated according to a number of oncology protocols (exact details not provided).<br><br>Episodes in which patients were discharged before their ANC was >500/$mm^3$ were retrospectively analysed to determine if they had indeed met the criteria for early discharge. |
| **Outcomes:**<br><br>Readmission related to prior febrile episode |
| **Results:**<br><br>Patients were characterised as being at relatively low risk if they had sterile blood cultures, were afebrile for > 24 hours, appeared well, and were thought to have evidence of marrow recovery.<br><br>330 episodes ended in discharge before the patient's ANC was ≥ 500/$mm^3$. At the time of discharge median ANC was 156/$mm^3$.<br><br>Of the 330 episodes, 21 (6%) were associated with admission for recurrent fever over the subsequent 7 days.<br><br>Six of the 21 (2% of the original 330) cases readmitted had evidence of bone marrow recovery.<br><br>None of the 21 had positive blood cultures.<br><br>All patients meeting low risk criteria fared well during their second hospitalisation. |
| **General comments:**<br><br>This retrospective study reviewed 580 consecutive episodes of chemotherapy induced |

febrile neutropenia in 253 children and adolescents with cancer. It had become common practice to discontinue therapy with broad spectrum antibiotics and discharge the patient before recovery from neutropenia if the child exhibited certain low-risk criteria. The article summarised centre's experiences. Patients had not received identical treatment. The sample size is however large enough to create an illuminating summary of the experience of implementing an early discharge policy. The authors concluded that the early discharge strategy was safe and resulted in substantial cost savings.

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| **Mullen, C. A. & Buchanan, G. R. (1990). Early hospital discharge of children with cancer treated for fever and neutropenia: identification and management of the low-risk patient. Journal of Clinical Oncology, 8, 1998-2004.** |
| **Country:**<br><br>USA |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>114 consecutive episodes of neutropenia in 61 patients treated between February 1988 and February 1999 |
| **Inclusion criteria:**<br><br>Age < 18 Neutropenia<br><br>(defined as ANC ≤ 500 cells per cubic milimeter) Fever (defined as<br><br>temperature of greater than 38°C for longer than 6 hours) |
| **Interventions:**<br><br>Initial treatment with broad spectrum cephalosporin antibiotic. There was no standard treatment protocol. Early discharge (with/without oral antibiotics) considered after being afebrile for 1-2 days if child had negative blood cultures, and (usually) if they had some evidence of bone-marrow recovery. |
| **Outcomes:**<br><br>Reoccurrence of fever |

| Re-hospitalisation |
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| **Results:**<br><br>77 (68%) patients were still neutropenic at the time of discharge after being afebrile for 1-2 days on parenteral antibiotics, had negative blood cultures, appeared well, and usually had some evidence of bone-marrow recovery.<br><br><u>Reoccurrence of fever / re-hospitalisation</u><br><br>3 (3.9%) of the 77 patients developed recurrent fever and required hospitalisation within 7 days of discharge. All had a brief uneventful second hospitalisation. |
| **General comments:**<br><br>Patients were treated according to a wide variety of Paediatric Oncology Group and institutional protocols. As a consequence the results do little to inform our understanding of any individual protocol/regimen. There was no written management protocol in place for early discharge, and records were reviewed to evaluate the safety of early discharge on the basis that "all attending physicians shared the philosophy of discharging children to home care as soon as they were afebrile and appeared well". The criteria for early discharge were vague. The authors conclude that the approach of routinely continuing hospitalisation until resolution of neutropenia may be unnecessary in low-risk patients. |

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| **Wacker, P., Halperin, D. S., Wyss, M., & Humbert, J. (1997). Early hospital discharge of children with fever and neutropenia: a prospective study. Journal of Pediatric Hematology/Oncology, 19, 208-211.** |
| **Country:**<br><br>Switzerland |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>88 consecutive cases of FN in 30 post-chemotherapy children (12 leukaemia and 18 solid tumours) entered into the study between May 1992 and May 1995 |

**Inclusion criteria:**

Neutropenia (defined as ANC<0.5x10$_9$/L)

Fever (temperature of ≥38.5°C on a single occasion, or 2 measurements ≥ 38.0°C in a 24 hour period)

**Interventions:**

IV antibiotics on admission:piperacillin (200mg/kg/day in four doses) and tamicin (5mg/kg/day in three doses) or imipenem (100mg/kg/day in four doses)

Children with FN divided into 3 groups:

Group A – *No documented infection* – discharged without antibiotics if afebrile for 24 hours with a normal physical exam. Outpatient visit scheduled within 48 hours, and CBC's were done every day until resolution of neutropenia. Parents monitored children 3 times a day and returned to hospital if fever recurred.

Group B – *Clinical or viral infection but no bacteremia* – some children who were afebrile for 24 hours with a normal physical exam were discharged with or without oral antibiotics. Outpatient visit scheduled within 48 hours, and CBC's were done every day until resolution of neutropenia. Parents monitored children 3 times a day and returned to hospital if fever recurred. Remainder stayed in hospital receiving IV antibiotics.

Group C – *Bacteremia* – Remained in hospital receiving IV antibiotics.

**Outcomes:**

Length of hospital stay

Recurrence of fever

Duration of fever before and after antibiotics

CBC values

**Results:**

<u>Group A (no infection)</u>

44 episodes (50%) occurred in 20 patients

Hospitalisation for a median of 4 days

On 25 occasions (57%), IV antibiotics were stopped before recovery of neutropenia.

2 children were re-hospitalised for recurrent FN but recovered without complications

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| Group B (clinically documented infection)<br><br>30 episodes (34%)<br><br>Early discharge was allowed in eight cases of minor infections (27%); six received oral antibiotics.<br><br>Group C (bacteremia)<br><br>14 episodes (16%) in 10 patients |
| **General comments:**<br><br>This was a prospective study of brief IV antibiotic therapy in selected children with cancer experiencing fever and neutropenia after chemotherapy. Episodes of FN were consecutive. Group assignment was based only on presence/absence of infection/bacteraemia, representing much simpler criteria than other studies. It is unclear what criteria were used to decide whether patients in group B were discharged "with" versus "without" oral antibiotics. Although length of hospital stay was stated as an outcome measure, this was not reported for groups B or C. The authors concluded that children hospitalised for fever without documented infections, and some children with minor infections can be discharged before evidence of bone marrow recovery if afebrile and in good general condition |

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| **Hodgson-Viden, H., Grundy, P. E., & Robinson, J. L. (2005). Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. *BMC Pediatrics, 5,* 10.** |
| **Country:**<br><br>Canada |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>276 episodes of FN in 127 patients |
| **Inclusion criteria:**<br><br>Age ≤ 17 years<br><br>Fever (defined as temperature ≥ 38.0°C at home or in hospital) |

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| Neutropenia (defined as ANC ≤ 500/$mm^3$) |
| **Exclusion criteria:**<br><br>Leukaemia not in remission |
| **Interventions:**<br><br>Details of exact treatment regimens are not given. 75% of patients were treated with IV piperacillin/tobramycin. Patients were discharged on the day intravenous antimicrobial therapy (IVAMT) was ceased. Early discharge was defined as discontinuation of IVAMT with an ANC ≤ 500/$mm^3$. |
| **Outcomes:**<br><br>Early discharge<br><br>Fever recurrence |
| **Results:**<br><br>112/199 (41%) patients were discharged before resolution of neutropenia<br><br>0 (0%) readmitted<br><br>0 (0%) died |
| **General comments:**<br><br>This was a retrospective review of medical records. The definition of a fever was less stringent than other studies, requiring only one measurement ≥ 38.0°C at home or in hospital. There was no use of standard criteria for early discharge. Decisions were said to be based solely on the clinician's judgement. On this basis, the study is not very informative. The authors concluded that clinicians were skilled at selecting |

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| **Griffin, T. C. & Buchanan, G. R. (1992). Hematologic predictors of bone marrow recovery in neutropenic patients hospitalized for fever: implications for discontinuation of antibiotics and early discharge from the hospital. Journal of Paediatrics, 121, 28-33.** |
| **Country:**<br><br>USA |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:** from April 1999 to November 1999 |
| **Inclusion criteria:**<br><br>Neutropenia (defined as ANC <500 cells/$mm^3$)<br><br>Fever (defined single temperature of at least 38.5°C or 38.0°C if persistent for 6 hours or longer) |
| **Exclusion criteria:**<br><br>Hospitalised for other reasons |
| **Interventions:**<br><br>Patients were given ceftazidime at a dosage of 150 mg/kg per day in three divided doses.<br><br>At the institution in question, patients did not necessarily remain in the hospital until recovery of neutropenia. Could be discharged early if:<br><br>1. Initial blood cultures were sterile after 48 hours<br>2. Appeared well<br>3. Any identified infection is under control<br>4. Fever absent for at least 24 hours.<br><br>Patients were given no oral antibiotic therapy<br><br>Daily CBCs were not performed after the patient's discharge.<br><br>Blood cultures were examined for 5 days before being classified as sterile. |
| **Outcomes:** |

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| Signs of early marrow recovery: total leukocyte count, absolute neutrophil count, absolute phagocyte count, and platelet count. |
| **Results:**<br><br>70/107 (65%) episodes were discharged with an absolute neutrophil count of fewer than 500 cells/$mm^3$<br><br>69/70 (99%) episodes had signs of early marrow recovery before discharge;<br><br>Sustained increases were observed in these patients' leukocyte, absolute neutrophil, absolute phagocyte, and platelet counts 2 or more days before their discharge in 41%, 49%, 50%, and 39% of cases, respectively.<br><br>None of the 69 patients who had evidence of marrow recovery at discharge had recurrence of fever. |
| **General comments:** This was a study conducted in the late 1980s. The aim was to evaluate the timing and pattern of changes in the complete blood cell count that preceded marrow recovery. Four measures derived from serial daily measurement of the complete blood cell count were evaluated: total leukocyte count, absolute neutrophil count, absolute phagocyte count, and platelet count.<br>The authors concluded that that children with cancer who were hospitalised for fever during periods of neutropenia have increases in the peripheral blood cell count that herald imminent bone marrow recovery, often several days before the absolute neutrophil count recovers to 500 cells/$mm^3$. |

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| **Nijhuis, C. O., Kamps, W. A., Daenen, S. M., Gietema, J. A., van der Graaf, W. T., Groen, H. J. et al. (2005). Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 23 (30)** |
| **Country:**<br><br>The Netherlands |
| **Design:**<br><br>Prospective consecutive case series |
| **Population:**<br><br>196 episodes of fever with chemotherapy induced neutropenia in 76 paediatric and |

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| adult patients between April 1999 and October 2002 |
| **Inclusion criteria:**<br><br>Fever (defined as single temperature ≥ 38.5°C, or two or more recordings ≥ 38.0°C during a 6-hour period).<br><br>Neutropenia (defined as ANC less than 0.5 x $10^9$/L or leukocytes less than 1.0 x $10^9$/L.<br><br>Written informed consent |
| **Exclusion criteria:**<br><br>Antibiotics during previous month<br><br>Stem cell transplant during previous month |
| **Interventions:**<br><br>All patients were admitted to hospital.<br><br>Patients with signs of a local bacterial infection and/or abnormal vital signs suggesting sepsis were classified as high risk. Abnormal vital signs indicating sepsis were defined as: systolic blood pressure less than 90 mmHg in adults or less than -2 SD for age in children, or both heart rate higher than 100/min and respiratory rate higher than 20/min in adults or both heart and respiratory rate higher than +2 SD for age in children.<br><br>Patients with plasma IL-8 level below the cut-off value were classified as low risk.<br><br>Patients with an IL-8 above the cut-off value were classified as medium risk.<br><br>For the first 75 episodes the cut off was 60 ng/L. It was then raised to 60 ng/L.<br><br>Low-risk patients did not receive intravenous antibiotics, except for those with severe mucositis who received oral amoxicillin-clavulanic acid. They were discharged once afebrile for 12 hours irrespective of their ANC. Following discharge, low-risk patients were contacted daily by the research physician until day 8 of the study protocol.<br><br>High-risk and medium-risk adults received intravenous cefuroxim (1,500 mg, three times daily) and tobramycin (3 mg/kg, once daily), and children ceftazidime (50 mg/kg, three times daily to a maximum of 6 g/d). Antibiotic treatment was stopped and patients were discharged when the blood culture was negative, patients were afebrile for at least 24 hours, and the ANC was greater than 0.5 x $10^9$/L. |

**Outcomes:**

Number of failures in the low-risk group (defined as either positive blood cultures at the time of admission, persistent fever, or recurrent fever in combination with prolonged neutropenia. Persistent fever was defined as a body temperature higher than 38.5°C for a minimum of 12 hours during the period of 48 to 72 hours after admission. Recurrent fever was defined as a new fever during the first 5 days of the study period, after having been afebrile for a minimum of 24 hours).

Diagnostic value of the risk assessment model (evaluated by assessing the sensitivity, specificity, and predictive values of the risk assessment model for the presence of bacteremia. Other secondary end points were duration of fever, neutropenia, intravenous antibiotic therapy, hospitalization (related to the febrile episode), and costs in the three risk groups).

**Results:**

<u>Low risk</u>

36 (18%) of patients

No intravenous antibiotics were given to patients in the low-risk group

0 failures

Median duration of hospitalisation: 3 days

*Diagnostic value:* Bacteremia was detected in none of the patients allocated to the low-risk group by the risk assessment model

Sensitivity of the risk assessment model was 100%

Specificity, positive predictive value, and negative predictive value were 21%, 13%, and 100%, respectively

<u>Medium risk group</u>

84 (43%) of patients

Intravenous antibiotic therapy was given for a median duration of 6 days in the medium-risk group

Median duration of hospitalisation: 7 days

<u>High risk group</u>

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| 76 (39%) of patients<br><br>Intravenous antibiotic therapy was given for a median of 6 days in the high-risk group<br><br>Median duration of hospitalisation: 7 days |
| **General comments:**<br><br>This was a prospective case series. A power calculation was presented. Adult and paediatric patients were included and analysed as one group. It was unclear what proportion of the sample were adults/children. Low risk criteria were changed after 75 episodes on the basis of a safety analysis. The authors concluded that the risk assessment model appeared to identify febrile neutropenic patients at low risk for bacterial infection, and that antibiotics could be withheld in well-defined neutropenic patients with fever. |

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| **Dommett, R., Geary, J., Freeman, S., Hartley, J., Sharland, M., Davidson, A. et al. (2009). Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. European Journal of Cancer, 45, 2843-2849.** |
| **Country:**<br><br>United Kingdom |
| **Design:**<br><br>Retrospective consecutive case series |
| **Population:**<br><br>762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005 |
| **Inclusion criteria:**<br><br>Age < 18 |

Neutropenia (defined as ANC < $1.0x10^9$/L)

Fever (single temperature of ≥ 38.5°C or sustained temperature of >38°C over 4 hours)

**Interventions:**

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 administered at the start of each FN episode and 48 hours later. Episodes were designated low risk if no risk factors were identified at either time point. All other episodes were designated standard risk. Fever at 48 hours did not exclude from the low risk strategy.

The checklist was as follows: Age<1 year, 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, peri-rectal or other soft tissue abscess, rigors, irritability/meningism, organ failure, acute lymphoblastic leukaemia at diagnosis/relapse <28 d, acute lymphoblastic leukaemia not in remission >28 d acute myeloid leukaemia, infant acute lymphoblastic leukaemia, intensive B-NHL protocols, haemopoietic stem cell transplant, sequential high dose chemotherapy with PBSC rescue, intensive care admission during last FN episode, non adherence (social concerns or patient), inability to tolerate oral antibiotics, positive blood culture result at 48 h, ANC < 0.1 · 109/L at 48 h, child not clinically well at 48 h (clinician judgement).

Low risk episodes: discharged at 48 h taking oral co-amoxiclav until 48 h after resolution of fever (<37.5ºC). 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. Patients remaining febrile at 96 hours were readmitted to hospital for intravenous antibiotics and amphotericin preparation. Children could also be readmitted at other times if concerns were raised.

**Outcomes:**

Hospital readmission

Intensive care admission

Mortality

**Results:**

In 40% of episodes no clinical or microbiological focus could be found.

At 48 hours, 212 (27%) of episodes were classified as low risk

143 (19%) were managed on the low risk protocol.

Hospital readmission

8 /143 (5.6%) were re-admitted to hospital

Intensive care admission

There were no intensive care admissions

Mortality

There were no deaths.

**General comments:**

This was a well conducted, reasonably large scale prospective study/audit of practice at four non-specialist paediatric oncology centres. Using a step-down strategy only 19% of patients were managed using the Low Risk protocol, despite 28% being eligible. The most common reason for failure to manage according to the low risk strategy was 'clinical decision'. The exact reasons for these decisions were not elaborated upon, but the authors suggest that there may have been a wariness to adopt the strategy, which may be remedied as data on the safety of the approach is disseminated. The authors concluded that 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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| **Santos-Machado, T. M., De Aquino, M. Z., Almeida, M. T. A., Bakhit, S., Cristofani, L. M., Maluf, P. T. et al. (99 A.D.). Short-term intravenous antibiotic therapy and early discharge of febrile neutropenic patients. International Journal of Pediatric Hematology/Oncology*, 6 (1) 33-38*** |
| **Country:**<br><br>Brazil |
| **Design:**<br><br>Retrospective consecutive case series |

**Population:**

79 consecutive episodes of febrile neutropenia in 46 paediatric inpatients from June to December 1996

**Inclusion criteria:**

Age < 18

Neutropenia (defined as APC < 1000/$mm^3$)

Fever (temperature of > 38°C)

**Interventions:**

Early discharge: IV antibiotic therapy (no details given) for 24 hours after defervescence if the following conditions met:

1. Negative blood cultures
2. No fever

In most cases patients were discharged with oral antibiotics. Followed up on an outpatient basis.

Customary procedure: IV antibiotic therapy for more than 24 hours. Discharged when APC recovery to 500 $mm^3$ minimum or after being on antibiotics for a minimum period of 72 hours after defervescence.

**Outcomes:**

Recurrence of fever

**Results:**

IV antibiotic therapy

Recurrence of fever

Early discharge: 4 (11.8%)

Customary procedure: 10 (22.2%)

There was no mortality

**General comments:**

This was a small scale retrospective study. No power calculation was reported. The definitions of fever and neutropenia were less stringent than in other studies. There was little detail provided with regards to treatment regimens. The authors did not report on the rate of hospital re-admission. The authors concluded that short term IV antibiotics could be safely used in FN patients with negative cultures and good clinical conditions.

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| **Innes, H., Lim, S. L., Hall, A., Chan, S. Y., Bhalla, N., & Marshall, E. (2008). Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. Supportive Care in Cancer, 16, 485-491.** |
| **Country:**<br><br>United Kingdom |
| **Design:**<br><br>Survey |
| **Population:**<br><br>128 clinicians representing 50 cancer departments |
| **Inclusion criteria:**<br><br>Consultant oncologists with an interest in antibiotic management of FN |
| **Outcomes:**<br><br>Use of tools to assess the risk of complications in FN patients<br><br>Use of oral antibiotics as a first-line treatment for patients with FN<br><br>Criteria used to determine suitability for discharge, and whether there are policies in place for early discharge |

**Results:**

38% of respondents stratify patients according to risk

There is substantial variation in the criteria defining 'low-risk'

Only one department (the author's) used structured pre-defined criteria

Only 22% of clinicians use oral antibiotics as first-line treatment in any patients with FN, but this was significantly greater among clinicians who do compared to those who do not stratify patients by risk, 51 vs 4% (P<0.0001).

84% of respondents confirmed their willingness to participate in a trial of oral antibiotics combined with early discharge in low-risk FN

**General comments:**

This was a survey of UK clinicians, aiming to determine whether recent advances in terms of risk stratification and the evolving role of oral antibiotics with early hospital discharge had been translated into clinical practice. The response rate was low (47.4%), and it is possible that those who routinely stratified patients according to risk were more likely to respond. Furthermore, respondent's from the author's own department were included, which may bias the results. The authors interpret the findings as suggesting a slow and/or cautious introduction of newer strategies for the management of low-risk FN in the UK.

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| **Castagnola, E., Paola, D., Giacchino, R., & Viscoli, C. (2000). Clinical and laboratory features predicting a favorable outcome and allowing early discharge in cancer patients with low-risk febrile neutropenia: a literature review. Journal of Hematotherapy & Stem Cell Research, 9, 645-649.** |
| **Country:**<br><br>Italy |
| **Design:**<br><br>Systematic review |
| **Population:**<br><br>27 studies including 5208 episodes of febrile neutropenia |
| **Inclusion criteria:**<br><br>Studies of febrile granulocytopenia in which a patient and disease oriented risk assessment led to identification of a low risk patients' subgroup |
| **Results:**<br><br>Favourable outcome (survival from febrile neutropenia) in more than 90% of episodes<br><br>7.4% needed rehospitalisation for any cause<br><br>Overall mortality of 87 (0.8%)<br><br>Features of low-risk patients who developed life-threatening infectious disease were related to general clinical condition, cancer control, bone marrow function, presence of clinical signs of infection, and social features. |
| **General comments:**<br><br>This review was published 11 years ago. Literature published in the previous 11 years was searched. Only one database (medline) was searched. A good range of search terms were used (neutropenia, fever, cancer, home-antibiotic therapy, short course of antibiotic therapy, and early discharge). The authors concluded that careful risk assessment could allow safe recognition of low-risk patients with febrile neutropenia who can be discharged early and can be used to follow outpatient treatment programs to improve patients' quality of life as well as the use of economic resources. |