Author(s): Baskaran *et al*., 2008

Country: Malaysia

Study participants:

68 patients with an underlying haematological malignancy admitted to a tertiary teaching hospital with febrile neutropenia between January 2004 and January 2005. The total number of febrile neutropenic admissions in these patients was 116. Median age: 40 years (range: 16-75 years).

Studies: N/A

Study Design:

Retrospective study. Data collected from in-patient and out-patient notes.

Definition of fever: single episode of oral temperature of 38.3°C or of 38°C lasting more than one hour.

Definition of neutropenia: neutrophils <500 cells per mm^3 or <1,000 cells per mm^3 with a predicted decrease to <500 cells per mm^3 within 48-72h.

Patients had to have received a course of chemotherapy prior to the episode of febrile neutropenia. Initial treatment for neutropenic fever on admission included: monotherapy with cefepime (Gram +ve and Gram –ve) then carbepenam on day 3 if there was deterioration, amphotericin B (anti-fungal) or vancomycin (Gram +ve). G-CSF was given to an unknown number of patients.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever without the development of serious medical complication or modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: hypotension (BP <90mm Hg), respiratory failure (O_2 pressure <60mm Hg), intensive care admission, disseminated vascular coagulation, confusion or altered mental status, congestive cardiac failure, bleeding requiring blood transfusion, ECG changes, arrhythmia requiring treatment, renal failure, other serious or clinically significant complications.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (5)
No COPD (4)
Solid tumour or no previous fungal infection (4)
No dehydration (3)
Burden of illness: moderate symptoms (3)

Outpatient status (3) Age <60 years (2) If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality. The 'burden of illness' was defined at length.
Results: 63% of the cases of febrile neutropenia had a favourable outcome. 16/68 patients died during follow-up and the overall mortality rate of total febrile episodes was 14%. Serious medical complications occurred in 34% of cases. Sensitivity: 93.2% Specificity: 67.4% Positive predictive value: 82.9% (False +ve rate =17.1%) Negative predictive value: 85.3% Prevalence of low risk in this study: 62.9% Five patients were thought to be at high risk but had favourable outcomes; all had been classified as having had a fungal infection but this could not subsequently be confirmed with cultures. Fourteen patients were classed as low risk but developed serious medical complications including Gram –ve sepsis with hypotension (n=6), severe mucositis with dehydration (n=3), Gram +ve sepsis (n=2), congestive heart failure (n=1) and respiratory failure following haemoptysis (n=1). **Length of stay:** Not reported. **Critical care:** Not reported.

Author(s): Carmona-Bayonas, 2008 **Country:** Spain
Study participants: 861 chemotherapy related FN episodes in adult outpatients (≥ 18 years) with solid tumours. Fever was defined as ≥ 38°C for at least an hour, neutropenia was ANC ≤ 0.5 x 10^9/L or ANC ≤ 1.0 x 10^9/L and predicted to fall to 0.5 x 10^9/L.
Study Design: Retrospective case series
Target Condition and reference standard: Serious complications as reported in medical records.
Tests: Multinational Association for Supportive Care in Cancer (MASCC) risk score: for scores ≥21 the patient was classified as being at low risk of serious complication

Results: MASCC <21 for the prediction of adverse events

TP	FP	FN	TN	Sn [95% C.I.]	Sp [95% C.I.]	prevalence high risk	LR+	LR-
112	7	32	18	0.78 [0.70, 0.84]	0.72 [0.51, 0.88]	0.15	2.78	0.31

Length of stay: Not reported.

Critical care: Not reported.

Author(s): Ammann, R. A., Bodmer, N., Hirt, A., Niggli, F. K., Nadal, D., Simon, A. *et al.,* (2010). - Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. - Journal of clinical oncology :28, 2008-2014.

Country: Switzerland and Germany

Study Design: Prospective observational study. No evidence to suggest randomisation**.**

Study participants: Paediatric cancer patients (1 - 18 years) of median age 6.9 years (IQR: 3.8-11.6) with neutropenia (ANC <0.5 X109/l) and fever (≥38.5°C or ≥38.0°C for ≥2 hours) after non-myeloablative chemotherapy. Multiple episodes were allowed. 472 episodes were reported in 206 patients.

Target condition/reference standard:

Adverse events: defined as serious medical complications, including death or the need for critical care as a result of infection, microbiologically documented infection or radiologically confirmed pneumonia.

Index tests and comparators: Figures from Phillips et al updated 2010 review update

Decision rule	TP	FP	FN	TN
Klaassen	106	155	16	146
Ammann	118	264	4	37
Alexander	115	275	7	26
PINDA	114	244	8	57

Follow up: Patients were assessed at presentation, then again after 8 to 24 hours of inpatient therapy. Length of follow up for adverse events was not reported.

Comments:

Patients had presented with febrile neutropenia at four centres between January 2004 and December 2007. The aim of the study was to develop a score to predict the risk of adverse events in young patients with cancer and neutropenic fever, comparing performance either at presentation or on a later reassessment. The investigators analysed the results using univariate

logistic regression to produce odds ratios for each predictor. There were 92 adverse events in 393 episodes.

Author(s): 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. Eur.J Cancer, 45, 2843-2849.

Country: UK

Study Design: Prospective audit.

Study participants: 762 episodes of febrile neutropenia in 368 paediatric patients from April 2004 to March 2005. Patients with haematologic and solid malignancies, 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)

Target condition/reference standard: The aim was to predict patients at low risk of serious bacterial infection who could be discharged safely. Reference standard was clinical or radiological evidence of serious bacterial infection

Index tests and comparators: Figures from Phillips et al updated 2010 review update

Decision rule	TP	FP	FN	TN
Alexander	131	226	92	311

Follow up: Risk was assessed at the start of each FN episode then reassessed 48 hours later.

Author(s): De Souza Viana *et al*., 2008 **Country:** Brazil
Study participants: 53 patients with underlying haematological malignancy (n=64%) or solid tumour (36%) with neutropenia and fever were recruited into this study at hospital between March and December 2004. Between them, the patients had 60 neutropenic episodes. Most patients (53%) were less than 60 years old.
Studies: N/A
Study Design: Prospective observational study. Definition of fever: axillary temperature of 38°C measured by the patient or medical staff.

Definition of neutropenia: absolute neutrophil count <500 cell per µl (including polymorphonuclear leukocytes and band forms) or absolute neutrophil count <1,000 per µl with a predicted decrease to <500 per µl within 24h.

Patients had to have received a course of chemotherapy and/or radiotherapy prior to the episode of febrile neutropenia. Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including an anti-pseudomonal ß-lactam in combination with an aminoglycoside or monotherapy with a third generation cephalosporin. G-CSF was given to 34 patients (risk group unknown).

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever without the development of serious medical complication or modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: arterial hypotension (BP <90mm Hg), respiratory failure (arterial O_2 pressure <60mm Hg, respiration >24 breaths per minute), intensive care admission, disseminated vascular coagulation, confusion or altered mental status, severe gastrointestinal disorders or sepsis, dehydration, bleeding requiring blood transfusion, platelet count <20,000 per µl, abnormal serum ions, bacteraemia, antibiotic treatment change secondary to recurrent or persistent fever, renal failure, other serious or clinically significant complications.

This study, in addition to using the MASCC score, sub-grouped low risk patients into those with or without complex infections in order to develop a new model. The data comparing MASCC with this unvalidated model are not considered further.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no0 or mild symptoms (5)
No hypotension (5)
No COPD (4)
Solid tumour or no previous fungal infection (4)
No dehydration (3)
Burden of illness: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Results:

Sensitivity: 85.0%

Specificity: 87.9%

Positive predictive value: 80.9% (False +ve rate =19.1%)

Negative predictive value: 90.6%

Prevalence of low risk in this study: 37.7%

Four patients considered to be at low risk developed serious medical complications due to respiratory distress (n=3) or dehydration (n=1). NB: the figures above are derived from the data given which were reported differently in the paper as the authors designated patients at high risk and the presence of complications as positive outcomes thus reversing sensitivity/specificity and PPV/NPV.

Length of stay: Median hospital stay: 7 days (range: 2-88 days). No comparative data reported.

Critical care: Seventeen patients were admitted to the ICU. No comparative data reported.

Author(s): Innes *et al*., 2008

Country: United Kingdom

Study participants:

83 patients with lymphoma (6%) or a solid tumour (94%) with neutropenia and fever were recruited into this study at a cancer centre between February and September 2003. Between them, the patients had 100 febrile neutropenic episodes. The median age of low risk patients was 53 years (range: 19-77) and of high risk patients 58 years (range: 33-75).

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: temperature of ≥38°C on at least two occasions (or 38.5°C on one occasion), measured (no more than once) by the patient or by medical staff.

Definition of neutropenia: absolute neutrophil count <500 cell per µl (including polymorphonuclear leukocytes and band forms) or absolute neutrophil count <1,000 per µl with a predicted decrease to <500 per µl within 24h-48h.

Low risk patients were given: ciprofloxacin (oral) plus co-amoxiclav or doxycycline or, if for some reason patients could not take oral drugs, were given intravenous ceftazidimine with the addition of vancomycin in the case of suspected line infection. High risk patients were given combination intravenous antibiotics including either gentamicin and Tazocin or gentamicin and ciprofloxacin. However, individual treating physicians were encouraged to use their discretion in applying the drug protocols.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either ‘favourable’ or ‘unfavourable’. ‘Favourable’ was defined as the resolution of fever within seven days without the development of serious medical complications and irrespective of

modification of initial antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: hypotension, respiratory/renal failure, intensive care admission, confusion or altered mental status, congestive cardiac failure, bleeding requiring blood transfusion, ECG changes, arrhythmia requiring treatment, development of fungal infection or an allergic reaction.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg)(5)
No COPD (4)
Solid tumour/lymphoma or no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)
Burden of illness: severe symptoms (0)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Results:

Sensitivity: 91.6%

Specificity: 40.0%

Positive predictive value: 96.7% (False +ve rate = 3.3%)

Negative predictive value: 20.0%

Prevalence of low risk in this study: 95.0%

One patient considered to be at low risk died after being readmitted due to progressive cancer. Two other patients at low risk developed severe medical complications: atrial fibrillation and perforation of the colon. The median hospital stay for low risk patients was 2.5 days compared with 6.5 days for high risk patients.

Length of stay: The median length of hospitalisation was 2.5 days (range: 0.5-12 days) in low risk episodes compared with 6.5 days (range: 0.3-11 days) in high risk episodes.

Critical care: Not reported.

Author(s): Ahn *et al*., 2010

Country: South Korea

Study participants:

346 patients with underlying haematological malignancy (n=28.5%) or solid tumour (71.5%) with neutropenia and fever were recruited into this study at the emergency department at a medical centre between January and December 2008. Between them, the patients had 396 neutropenic episodes. The median age of patients was 55 years.

Studies: N/A

Study Design:

Retrospective observational study.

Definition of fever: single oral temperature of ≥38.3°C or of >38.0°C for ≥1 hr.

Definition of neutropenia: absolute neutrophil count <500 cell per mm^3 or a count of <1,000 per mm^3 with a predicted decrease to <500 per mm^3 within an undefined time.

Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including an anti-pseudomonal ß-lactam in combination with an aminoglycoside or monotherapy with a third generation cephalosporin. G-CSF was given to 95.4% of patients who had a favourable outcome group and 91.8% of patients who had an unfavourable outcome.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable'. 'Favourable' was defined as the resolution of fever for five consecutive days without the development of serious medical complications and irrespective of modification of antibiotic therapy. 'Unfavourable' was defined as the resolution of fever with at least one serious medical complication, including death. 'Serious medical complications' were defined at length but briefly included: refractory hypotension despite fluid therapy, respiratory failure requiring intubation, intensive care admission, disseminated intravascular coagulation, confusion or altered mental status, congestive cardiac failure, ECG changes requiring anti-arrhythmic treatment, renal failure and other complications judged serious and clinically significant by the investigator.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Result: Sensitivity: 95.4% Specificity: 52.1% Positive predictive value: 89.8% (False +ve rate = 10.2%) Negative predictive value: 71.7% Prevalence of low risk in this study: 81.6% NB: the figures above are derived from the data given which were reported differently in the paper as the authors designated patients at high risk and the presence of complications as positive outcomes thus reversing sensitivity/specificity and PPV/NPV. Of 343 events defined as low risk by the MASCC score, 35 (10.2%) were associated with serious medical complications including 5 deaths due to sepsis. **Length of stay:** Not reported. **Critical care:** Not reported.

Author(s): Uys *et al*., 2007 **Country:** South Africa
Study participants: 63 patients with underlying haematological malignancy (30%) or a solid tumour (70%) with neutropenia and fever were recruited into this study at a cancer centre at an unknown period before 2006. Between them, the patients had 78 neutropenic episodes. The median age of patients was 50 years.
Studies: N/A
Study Design: Prospective observational study. The main aim of the study was to compare various laboratory parameters with the MASCC score in the identification of low risk patients with febrile neutropenia. The results of this comparison are not presented here. Definition of fever: single oral temperature of ≥39°C or of >38.0°C on two separate occasions at least four hours apart. Definition of neutropenia: absolute neutrophil count <500 cell per µl. Initial treatment for neutropenic fever on admission included: broad-spectrum antibiotics including

cefepime/ceftriaxone plus amikacin (one patient received meropenum monotherapy). Patients not responding to this empirical therapy were given vancomycin. Patients with persistent fever were also given amphotericin B. G-CSF was given during 26 episodes of febrile neutropenia (17 low risk patients).

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'favourable' or 'unfavourable, including death'. 'Serious medical complications' were defined at length but briefly included: hypotension, respiratory/renal/congestive cardiac failure, intensive care admission, confused mental status, bleeding requiring transfusion, allergic reaction, ECG changes and arrhythmia requiring treatment.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of illness: no or mild symptoms (5)
No hypotension (systolic BP >90mm Hg) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of illness: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.

Result:

These values are as reported by the authors but could not be verified as outcome data regarding the numbers of patients in low or high risk groups who experienced serious medical complications were not reported

Sensitivity: 95%

Specificity: 95%

Positive predictive value: 98.3% (False +ve rate = 1.7%)

Negative predictive value: 86.4%

Prevalence of low risk in this study: 72.5%

Length of stay: Not reported.

Critical care: Four patients in the high risk group were admitted to ICU.

Author(s): Klastersky *et al*., 2006

Country: Belgium

Study participants:

All patients older than 16 years with underlying haematological malignancy (4%) or a solid tumour (96%) with neutropenia and fever were assessed by the MASCC score between January 1999 and November 2003 at a single hospital. Those patients classed as 'low risk' and eligible for oral antibiotic treatment were entered into this study and had between them 189 neutropenic episodes of which 178 first episodes. The median age of those patients was 53 years (range: 17-85 years).

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: single oral temperature of ≥38.5°C or of >38.0°C on two separate occasions during a 12 hour interval.

Definition of neutropenia: absolute neutrophil count <500 cell per µl or a count of <1,000 per µl with a predicted decrease to <500 per µl within 24 to 48 hours.

Patients with a first febrile neutropenic episode deemed to be low risk according to their MASCC score were treated by oral antibiotics, if not already on prophylactic treatment at fever onset, and were hospitalised for 24 hours under close clinical and microbiological surveillance. Where appropriate, patients could then be discharged to continue treatment and self monitoring at home, returning every two days for testing until the resolution of fever. Oral treatment included: ciprofloxacin and amoxicillin-clavulanate. A low number of patients (n=11) were instead given a quinolone with or without other antibiotics.

Target Condition:

The primary endpoint of this study was to assess the safety of the early discharge procedure with low risk patients. However, the report also included data that enabled sensitivity and specificity of the MASCC score to be determined.

'Serious medical complications' included those from a previous publication, namely: hypotension (BP <90mm HG), respiratory failure, ICU admission, intravascular coagulation, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmia or ECG changes needing treatment, renal failure requiring intervention or other complications judged serious and clinically significant.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of febrile neutropenia: no or mild symptoms (5)
No hypotension (BP >90mm HG) (5)
No COPD (4)

Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of febrile neutropenia: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality. The 'burden of illness' and other items were defined at length.

Results:

79/178 low risk patients with first neutropenic episode were treated with oral antibiotics and discharged early. Of these, none experienced serious medical complications as defined above but three were re-admitted with: stomatitis and oesophagitis with change to intravenous therapy, persistent fever without therapy change and chills with change to intravenous antibiotics. The success rate of the early discharge policy was therefore 76/79 (96%). 9/178 patients had serious medical complications including: death (n=2) anaemia (n=1), hypotension with other factors (n=4), respiratory failure and confusion (n=1) and renal failure with other factors (n=1).

Of all 441 neutropenic episodes classed as low risk, the resolution rate was 88% (95%CI: 84-91%). Of the 170 neutropenic episodes classed as high risk, the resolution rate was 64% (95%CI: 56-71%). From these figures the following are computed but may not be accurate:
Sensitivity: 78.1%

Specificity: 53.5%

Positive predictive value: 88.0% (False +ve rate = 12.0%)

Negative predictive value: 35.9%

Prevalence of low risk in this study: 81.3%

Length of stay: If a patient stayed in hospital for <2 days it was classed as early discharge. 79 (44%) low risk patients were discharged early (median time to discharge: 26 hours) whereas 99 low risk patients remained hospitalised (median time to discharge: 137 hours). Data for high risk patients were not reported.

Critical care: Not reported.

Author(s): Hui *et al*., 2010

Country: Hong Kong

Study participants:

227 patients over the age of 16 years with underlying haematological malignancy (20.3%) or a solid tumour or lymphoma (79.7%) with neutropenia and fever were recruited into this study at a tertiary cancer centre between October 2005 and February 2008. The median age of patients was 51 years and 28.6% were aged ≥60.

Studies: N/A

Study Design:

Prospective observational study. The purpose of this study was not only to validate the MASCC scoring system but to compare it with an artificial neural network model of the authors' design. These comparative data are not presented here.

Definition of fever: single temperature of ≥38.3°C or of >38.0°C on two occasions ≥1 hr apart.

Definition of neutropenia: absolute neutrophil count <500 cell per mm^3 or a count of <1,000 per mm^3 with a predicted decrease to <500 per mm^3 within an undefined time.

Initial treatment for neutropenic fever on admission included empirical intravenous antibiotics according to the institutional guidelines. There were no further details.

Target Condition:

The dependent variable of interest was the final outcome of each febrile neutropenic episode, either 'good' or 'poor'. 'Good' was defined as the resolution of fever for five consecutive days without the development of serious medical complications and irrespective of modification of antibiotic therapy. 'Poor' was defined as the resolution of fever for five consecutive days with at least one serious medical complication, including death or death before fever resolution.

'Serious medical complications' included those from the original MASCC study namely: hypotension (BP <90mm HG), respiratory failure, ICU admission, intravascular coagulation, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmia or ECG changes needing treatment, renal failure requiring intervention or other complications judged serious and clinically significant.

Tests:

Multinational Association for Supportive Care in Cancer (MASCC) risk score:

Burden of febrile neutropenia: no or mild symptoms (5)
No hypotension (BP >90mm HG) (5)
No COPD (4)
Solid tumour or haematological malignancy with no previous fungal infection (4)
No dehydration requiring parenteral fluids (3)
Burden of febrile neutropenia: moderate symptoms (3)
Outpatient status (3)
Age <60 years (2)

If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality. The 'burden of illness' and other items were defined at length.

Results:

Sensitivity: 81.1%

Specificity: 60.3%

Positive predictive value: 85.6% (False +ve rate = 14.4%)

Negative predictive value: 52.2%

Prevalence of low risk in this study: 74.4%

160 patients were defined by the MASCC score as being 'low risk' and 67 as 'high risk'. In the low risk group, 20 patients experienced complications and 3 patients died. In the high risk group, 29 patients experienced complications and 6 patients died. There were no further details of the nature of these complications or of the causes of death.

Length of stay: Not reported

Critical care: Not reported

Author(s): Cherif *et al*., 2006

Country: Sweden

Study participants:

191 patients over the age of 16 years with underlying haematological malignancies with neutropenia and fever were recruited into this study at a cancer unit between November 2003 and April 2005. The median age of patients in the high risk group was 60 years (range: 21-85 years) and in the low risk group 57 years (range: 20-87 years).

Studies: N/A

Study Design:

Prospective observational study.

Definition of fever: temperature (oral or in the ear) of ≥38.0°C on two occasions ≥4 hr apart or ≥38.5°C on a single occasion.

Definition of neutropenia: absolute neutrophil count <500 cell per mm^3.

Initial treatment for neutropenic fever on admission included broad-spectrum intravenous antibiotics, in accordance with local and international recommendations, until the fever subsided. G-CSF was not routinely given but was administered to 29% of high risk patients and 36% of low risk patients. Patients deemed to be low risk according to their MASCC score and who did not develop shock, catheter-related infection, multi-resistant infection or invasive fungal infection were considered for oral therapy 24 hours after fever had subsided. After the first dose, some of these patients were discharged and continued oral treatment at home.

Target Condition:

Patients were monitored daily for clinical complications. 'Serious medical complications' included: death, hypotension, respiratory failure, requirement for intensive care, confusion or altered mental state, congestive heart failure, bleeding severe enough to need transfusion, arrhythmias needing

treatment, fungal infection, allergic reaction, renal failure or other complications judged serious and clinically significant.
Tests: Multinational Association for Supportive Care in Cancer (MASCC) risk score: Burden of febrile neutropenia: no or mild symptoms (5) No hypotension (5) No COPD (4) No previous fungal infection (4) No dehydration (3) Burden of febrile neutropenia: moderate symptoms (3) Outpatient status at the time of fever onset (3) Age <60 years (2) If the sum of these characteristics ≥21 the patient was classified as being at low risk of complication or mortality.
Result: Sensitivity: 58.6% Specificity: 87.4% Positive predictive value: 84.8% Negative predictive value: 63.8% Prevalence of low risk in this study: 54.5% Serious medical complications occurred in 111/174 episodes in high risk patients and 16/85 episodes in low risk patients. The most commonly occurring complications in high risk patients were: hypotension (21%), respiratory failure (22%), invasive or superficial fungal infection (28%) and allergic reaction (14%). Death occurred in 10 high risk patients due to: septic shock (n=3), pneumonia (n=2), pulmonary aspergillosis (n=1) and other, unnamed causes (n=4). Death occurred in 2 low risk patients from: septic shock (n=1) and pneumonia (n=1). **Length of stay:** Low risk patients who were able to be treated with oral antibiotics had a significantly shorter stay in hospital (6 ± 4 days) compared with high risk patients (16 ± 13 days) (P<0.0001). Those low risk patients who were discharged early spent fewer days in hospital (2.2 ± 1.8). **Critical care:** 10 patients in the high risk group had to be admitted to ICU compared with 0 patients in the low risk group (P<0.01).

Author(s): Phillips *et al*., 2010

Country: United Kingdom

Included studies: Prospective and retrospective cohort studies (not case controls) either published or unpublished. No language restriction.

Study participants: The intended study population was children or young people (aged 0-18 years) presenting with febrile neutropenia. The included studies reported on patients from 1 month to 23 years old.

Study Design:

The aim of this paper was to review evidence on the ability of existing clinical decision rules to risk stratify children and young people presenting with febrile neutropenia. Included studies reported on either two (low and high) or three (low, medium and high) risk categories the data for which were analysed statistically by different methods and software. Where observed, between studies heterogeneity was explored and sensitivity analyses were performed.

Results:

There were 8 prospective and 11 retrospective studies plus one retrospective analysis of prospectively collected data. Between them, these studies reported nearly 8,000 episodes of febrile neutropenia and described eleven outcomes which the reviewers summarised into five clusters: death, need for critical care, serious medical complications, significant bacterial infection or bacteraemia.

Most studies could not be pooled as they differed too much from one another in terms of rules, outcomes, locations and populations. However, data from multiple studies validated two existing rules (Rackoff rule with an outcome of 'bacteraemia' and the Santolaya rule with an outcome 'invasive bacterial infection') and were combined in two meta-analyses. For each outcome a likelihood ratio (LR) was calculated with 95% credibility (post-test probability) or confidence intervals.

- **Rackoff rule:** [Low risk: absolute monocyte count >100; mid risk: absolute monocyte count <100 with temperature <39°C; high risk: absolute monocyte count <100 with temperature ≥39°C]**:**

LR [low risk] = 0.22 (95%CrI: 0.03-1.85)

LR [medium risk] = 0.79 (95%CrI: 0.12-2.06)

LR [high risk] = 3.41 (95%CrI: 0.24-18.7)

Assuming a 22% overall prevalence of bacteraemia:

Predictive value [low risk] = 6% (95%CrI: 1-34%)

Predictive value [medium risk] = 18% (95%CrI: 3-37%)

Predictive value [high risk] = 49% (95%CrI: 6-84%)

- **Santolaya rule:** [Low risk: 0 factors or isolated low platelets or >7 days from chemotherapy;

High risk: >1 risk factor or isolated high CRP, hypotension or relapsed leukaemia. Risk factors: CRP ≥90, hypotension, relapsed leukaemia, platelets ≤50, chemotherapy within 7 days].

LR [low risk] = 0.17 (95%CI: 0.12-0.23)

LR [high risk] = 2.87 (95%CI: 0.24-18.7)

Assuming a 47% overall probability of invasive bacterial infection :

Predictive value [low risk] = 13% (95%CI: 9-13%)

Predictive value [high risk] = 72% (95%CI: 68-75%)

Across all studies, the clinical decision rules (CDR) fell into four broad categories: patient-related factors (such as age, disease state) treatment (such as the time since last chemotherapy cycle) clinical features specific to the episode (such as temperature, blood pressure) and laboratory values relating to the episode (such as blood components, CRP). Common features across all studies show that age, malignant disease state, circulatory and respiratory distress, high temperature and bone marrow suppression all had some predictive power.

Comments:

This high quality systematic review and meta analysis reports the findings from 21 journal articles. The search strategy was described in detail (http://www.ejcancer.info/article/S0959-8049(10)00448-X/addOns). Searches were made from ten databases including MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Titles were independently screened and disagreements resolved by consensus. Study quality was assessed using a modified QUADAS checklist.

Included studies:

Adcock KG, Akins RL, Farrington EA. (1999). Evaluation of empiric vancomycin therapy in children with fever and neutropenia. *Pharmacotherapy* **19(11):** 1315–20.

Alexander SW, Wade KC, Hibberd PL, Parsons SK. (2002). Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. *J Pediatr Hematol/Oncol* **24(1):** 38–42.

Ammann RA, Hirt A, Luthy AR, Aebi C. (2003) Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. *Med Pediatr Oncol* **41(5):** 436–43.

Baorto EP, Aquino VM, Mullen CA, Buchanan GR, DeBaun MR. (2001). Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer* **92(4):** 909–13.

Gala Peralta S, Cardesa Salzman T, Garcia Garcia JJ, et al. (2005). Bacteraemia risk criteria in the paediatric febrile neutropenic cancer patient. *Clin Transl Oncol* **7(4):** 165–8.

Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A (1997). Comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* **99(3):** 580–8.

Jones GR, Konsler GK, Dunaway RP, Pusek SN. (1996) Infection risk factors in febrile, neutropenic children and adolescents. *Pediatr Hematol Oncol* **13(3):** 217–29.

Klaassen RJ, Goodman TR, Pham B, Doyle JJ. (2000) ''Low-risk'' prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clin Oncol **18(5):** 1012–9.

Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. (1996) The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer* **77(4):** 791–8.

Madsen K, Rosenman M, Hui S, Breitfeld PP. (2002) Value of electronic data for model validation and refinement: bacteremia risk in children with fever and neutropenia. *J Pediatr Hematol/Oncol* **24(4):** 256–62.

Paganini HR, Aguirre C, Puppa G, et al. (2007) A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer* **109(12):** 2572–9.

Petrilli AS, Melaragno R, Bianchi A, et al. (1991) Fever and neutropenia in children with cancer: a new therapeutic proposal. *Amb; Rev Assoc Med Bras* **37(4):** 173–80.

Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PB. (1996) Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* **14(3):** 919–24.

Riikonen P, Jalanko H, Hovi L, Saarinen UM. (1993) Fever and neutropenia in children with cancer: diagnostic parameters at presentation. *Acta Paediatr Int J Paediatr* **82(3):** 271–5.

Rojo LC, Rodriguez ZN, Tordecilla CJ. (2008) Low risk febrile neutropenia in oncological pediatric patients: clinical experience [Spanish]. *Rev Chilena Pediatr* **79(2):** 157–62.

Rondinelli PIP, Ribeiro KdCB, de Camargo B. (2006) A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J Pediatr Hematol/Oncol* **28(10):** 665–70.

Santolaya ME, Alvarez AM, Avils CL, et al. (2002) Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. *Clinical Infectious Diseases* **35(6):** 678–83.

Santolaya ME, Alvarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol 2001* **19(14):** 3415–21.

Tezcan G, Kupesiz A, Ozturk F, et al. (2006) Episodes of fever and neutropenia in children with cancer in a tertiary care medical center in Turkey. *Pediatr Hematol Oncol* **23(3):** 217–29.

West DC, Marcin JP, Mawis R, et al. (2004) Children with cancer, fever, and treatment-induced neutropenia: risk factors associated with illness requiring the administration of critical care therapies. *Pediatr Emerg Care* **20(2):** 79–84.

Author(s): Macher *et al*. (2010)

Country: France

Study participants:

167 paediatric patients with haematological malignancy (59% of episodes) or solid tumours (41% of episodes) were admitted to either a cancer centre or children's hospital between January 2005 and December 2006. The total number of consecutive febrile neutropenic episodes in these children was 381 of which 377 were included for analysis. The median age of patients was 6yrs, mean age: 7.2yrs (range: 7mo – 19yrs).

Studies: N/A

Study Design:

Retrospective cohort study (two-centre).

Definition of fever: single axillary temperature of ≥38.5°C or 38°C on two occasions over a period of one hour.

Definition of neutropenia: absolute neutrophil count <500 cells per µl.

All patients were admitted and received intravenous antibiotics including a broad spectrum ß-lactam and an aminoglycoside. Some children experienced FN whilst already in hospital but children were excluded if they had had a bone marrow or stem cell transplant, were receiving palliative care or had already received antibiotics during the episode of FN prior to admission.

Target Condition:

The clinical outcomes were 'severe bacterial infection' (SBI), including invasive fungal infection, and bacteremia, including fungemia. The definitions applied to these outcomes were taken from each study.

Tests:

A comparison of six clinical decision rules in their ability to predict clinical outcomes of children admitted with febrile neutropenia. These rules were:

Rackoff *et al*. (1996): low risk of bacteremia: absolute monocyte count (AMC) ≥100 per µl at admission

Baorto *et al*. (2001): low risk of bacteremia: AMC >155 per µl at admission

Klaassen *et al.* (2000): low risk of SBI: AMC >100 per µl at admission

Santolaya *et al.* (2001): high risk of SBI: serum CRP AMC ≥90 mg per litre at admission; hypotension; relapse of leukaemia; platelets ≤50,000 per µl; chemotherapy within 7 days of hospital visit. Otherwise low risk.

Ammann *et al.* (2003): high risk of SBI: bone marrow involvement by malignancy or a leukocyte

count ≤500 per µl or no sign of viral infection or aged >6 years.

Rondinelli *et al.* (2006). For the first neutropenic episode, risk of SBI: presence of central catheter, clinical site of infection, fever ≥38.5°C, haemoglobin at admission ≤7 g per dl; upper respiratory tract infection.

Results:

Bacteraemia occurred in 36/377 episodes (10%) and serious bacterial infection in 64/377 episodes (17%). The performance for each rule was calculated using that rule's definitions for the outcomes 'bacteraemia' or 'serious bacterial infection'. These two outcome definitions were also 'homogenised' in order to make the results from the different studies comparable (see Table below).

Study (no of episodes)	Sensitivity % (± 95%CI)	Specificity % (± 95%CI)	PPV % (± 95%CI)	NPV % (± 95%CI)	LR+	LR-
Rackoff *et al.*, 1996 (n=134)	87 (62-96)	44 (35-53)	16 (10-26)	96 (87-99)	1.3	0.3
Baorto *et al.*, 2001 (n=174)	96 (79-99)	25 (19-33)	16 (11-23)	97 (87-100)	1.3	0.2
Klaassen *et al.*, 2000 (n=138)	79 (61-90)	45 (36-54)	27 (18-37)	89 (78-95)	1.4	0.5
Santolaya *et al.*, 2001 (n=249)	67 (53-80)	39 (33-46)	19 (13-26)	85 (77-91)	1.1	0.8
Ammann *et al.*, 2003 (n=371)	95 (87-98)	5 (3-8)	17 (13-21)	83 (61-94)	1.0	1.0
Rondinelli *et al.*, 2006 (n=121)	62 (36-82)	43 (35-52)	11 (6-21)	90 (79-96)	1.1	0.9

From Table ( ), the rule with the best predictive ability for 'bacteraemia was that of Baorto *et al.* (2001) and for 'SBI', Ammann *et al.* (2003) although the specificity was very low.

Using each rule's definitions, thresholds and risk factors, the current data set showed similar sensitivity to all studies but Santolaya *et al.* (2001) (non-overlapping confidence intervals) or Rondinelli *et al.* (2006) (performance data not reported). The specificity was only similar to Klassen *et al.* (2000).

Comments:

None of the studies met the required 100% sensitivity which the authors had thought necessary in order to safely apply a rule to this population. The two studies that came closest still failed to identify one or two patients deemed to be at low risk who developed bacteraemia or SBI.

The authors concluded that, given the high number of clinical variables in children with febrile neutropenia, identifying a single set of rules that could reliably classify low risk had not proved to be possible.

Papers included in this review:

Rackoff WR, Gonin R, Robinson C, *et al.* (1996). Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* **14:** 919–924.

Baorto EP, Aquino VM, Mullen CA, *et al*. (2001). Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer* **92:** 909–

913.

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Santolaya ME, Alvarez AM, Becker A, *et al*. (2001) Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol* **19:** 3415–3421.

Ammann RA, Hirt A, Lüthy AR, *et al.* (2003) Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. *Med Pediatr Oncol* **41:** 436–443.

Rondinelli PI, Ribeiro Kde C and de Camargo B. (2006) A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J Pediatr Hematol Oncol* **28:** 665–670.