Author(s): Ammann *et al.* (2003)

Country: Switzerland

Study Design: Retrospective observational study.

Study participants: Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after myelosuppressive chemotherapy. There were 285 FN episodes in 111 children. Median age at the first FN episode was 6.3 years. The proportion with haematological cancers was not reported.

Target condition/reference standard:

Severe (significant) bacterial infection defined as: bacteraemia, positive urine culture, pneumonia, clinically unequivocal diagnosis of infection, serum CRP >150mg/L or unexpected death from infection.

Index tests and comparators:

(i) Maximum fever at presentation: ≤39°C versus >39°C

(ii) General appearance at presentation: not reduced versus slightly reduced

(iii) General appearance at presentation: not reduced versus severe reduced

(iv) Chills at presentation: no versus yes

(v) Oral mucositis at presentation: no (or slight) versus severe

(vi) Clinical signs of viral infection: no versus yes.

Follow up: Not reported.

Comments:

Patients had presented with febrile neutropenia at a single centre between January 1st 1993 and 31st December 2001. The aim of the study was to predict severe bacterial infection in young patients presenting with neutropenia and fever. Of thirty-nine covariates, six were relevant to this question. There were missing values for some covariates: fever (N=4), appearance (N=49), chills (N=2), mucositis (N=33) and signs of viral infection (N=1). The rate of severe bacterial infection was 106/285 (37%). Note that the confidence intervals were 99% to allow for multiple comparisons.

(i) OR 1.62 (99%CI: 0.83-3.18) TP(true positive) =62, FP(false positive)=83, FN (false negative)=44, TN (true negative)=92

(ii) OR 1.33 (99%CI: 0.56-3.35) TP=54 FP=99 FN=18 TN=44

(iii) OR 1.50 (99%CI: 0.32-6.51) TP=8 FP=13 FN=18 TN=44

(iv) OR 3.07 (99%CI: 0.71-15.6) TP=10 FP=6 FN=93 TN=174

(v) OR ∞ (99%CI: ∞-1.54) TP=3 FP=0 FN=83 TN=166

(vi) OR 2.05 (99%CI: 0.96-4.57) TP=22 FP=63 FN=84 TN=115

Author(s): Ammann *et al.* (2004) **Country:** Switzerland
Study Design: Retrospective observational study.
Study participants: Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after myelosuppressive chemotherapy. There were 364 FN episodes in 132 children.
Target condition/reference standard: Bacteremia, defined as: at least one positive blood culture using a qualitative automated culture system (BacT/ALERT by bioMérieux). The authors were particularly interested in the incidence of Gram –ve infection.
Index tests and comparators: (i) Maximum fever at presentation: <39.7°C versus >39.7°C (ii) Chills at presentation (iii) No clinical evidence of viral infection.
Follow up: Not reported.
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 1993 and 31st December 2001. The aim of the study was to predict the risk of bacteremia in young patients presenting with neutropenia and fever. Of forty-four covariates, one was relevant to this question. The rate of bacteremia in the first episode only was 85/348 and there were 30

episodes of Gram –ve bacteremia. The majority of patients (N=285) in this study overlapped with those in Ammann *et al*., 2003 but, in this case, the 79 patients who had presented with known serious bacterial infection are included since the outcome of interest (bacteremia) is different.

Risk of bacteremia:

(i) OR 3.2 (95%CI: 1.5-7.1) TP=16 FP=17 FN=69 TN=246

Risk of Gram –ve bacteremia:

(ii) OR 3.5 (95%CI: 1.3-9.7) Sensitivity and specificity could not be derived from the data.

(iii) OR 3.6 (95%CI: 1.1-19.0). Sensitivity and specificity could not be derived from the data.

Author(s): Ammann *et al.* (2010) **Country:** Switzerland
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 $X10^9$/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: At presentation, without adverse events known: (i) General condition severely reduced versus not (ii) Oral mucositis present to any degree versus not (iii) Other mucositis present to any degree versus not (iv) Clinical signs of upper respiratory infection versus not (v) Axillary temperature >39.5°C versus not

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.

At presentation, without adverse events known (N=393):

(i) OR 2.3 (95%CI: 1.2-4.7) (P=0.019)* TP=14 FP=23 FN=78 TN=278

(ii) OR 0.6 (95%CI: 0.4-1.0) (P=0.070) TP=26 FP=121 FN=66 TN=180

(iii) OR 0.9 (95%CI: 0.5-1.9) (P=0.84) TP=10 FP=37 FN=82 TN=264

(iv) OR 0.9 (95%CI: 0.5-1.6) (P=0.72) TP=21 FP=76 FN=71 TN=225

(v) OR 2.8 (95%CI: 1.2-6.4) (P=0.015)* TP=11 FP=14 FN=81 TN=287

*These characteristics were used as part of a multivariate prediction model.

Author(s): Chayakulkeeree *et al.* (2003) **Country:** Thailand
Study Design: Retrospective observational study.
Study participants: Adult or adolescent patients (>12 years, mean age 44.7 years) with febrile (>38°C) neutropenia (<500/mm^3). Nearly half (45%) the patients were male. There were 267 episodes in 220 patients. 158/220 (72%) patients had a haematological malignancy. Episodes were: clinically documented infection (N=38), microbiologically documented infection (N=90) or fever of unknown origin (N=139).
Target condition/reference standard: Favourable outcome: fever resolved in 5 days of starting treatment and without complications Unfavourable outcome: Death, serious complications, modification of initial therapy, relapse of resolved fever or fever longer than 5 days. The reference standard was clinical follow up as reported in patients' medical records.

Index tests and comparators:

(i) Temperature ≥39°C versus <39°C

(ii) Altered mental state versus not

(iii) Mucositis versus not

(iv) Diarrhoea versus not

(v) Abdominal pain versus not

(vi) Nausea and vomiting versus not

Follow up: Five days

Comments:

Patients had presented with febrile neutropenia at a single centre between January 1999 and December 2000. The aim of the study was to identify types of infection and the causative organisms; also to validate a risk score.

(i) OR 1.37 (95%CI: 0.84-2.23) (P=0.263) TP=83 FP=48 FN=76 TN=60

(ii) OR 4.21 (95%CI: 1.62-10.94) (P=0.004) TP=27 FP=5 FN=132 TN=103

(iii) OR 3.21 (95%CI: 1.73-5.95) (P<0.001) TP=57 FP=16 FN=102 TN=92

(iv) OR 3.26 (95%CI: 1.65-6.43) (P=0.001) TP=46 FP=12 FN=113 TN=96

(v) OR 3.08 (95%CI: 1.32-7.18) (P=0.014) TP=28 FP=7 FN=131 TN=101

(vi) OR 1.63 (95%CI: 0.81-3.27) (P=0.232) TP=29 FP=13 FN=130 TN=95

Author(s): Hakim *et al.* (2010) **Country:** United States of America
Study Design: Retrospective observational study
Study participants: Paediatric cancer patients (up to 22 years) with neutropenia (ANC <500/mm^3 or <1000/mm^3 and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours). Median age was 6 years (2.4 months – 21.6 years). There were 332 FN episodes in 332 children (one episode per patient was selected at random from the records).

Target condition/reference standard: Invasive bacterial infection: bacteraemia, positive urine culture or culture negative sepsis
Index tests and comparators: (i) Temperature ≥39°C versus <39°C (ii) Clinical appearance: sick/toxic versus well. This variable was adjudged by the admitting physician. 'Well' was defined as 'looking well, in no distress or playful'; 'Sick if 'noted to be irritable, or looking ill' and 'toxic' if 'not breathing or noted to appear toxic, lethargic or obtunded'.
Follow up: N/A
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 2004 and 31st December 2005. (i) OR 2.05 (95%CI: 1.00-4.20) TP=28 FP=91 FN=28 TN=183 (ii) OR 3.84 (95%CI: 2.02-7.28) TP=28 FP=55 FN=29 TN=219

Author(s): Klaassen *et al.* (2010) **Country:** Canada.
Study Design: Prospective observational study (consecutive data)
Study participants: Paediatric cancer patients (≤ 18 years) receiving cancer chemotherapy with neutropenia (ANC <500/mm^3 or <1000/mm^3 and expected to fall) and fever (≥38.5°C or multiple readings ≥38.0°C in a 12 hour period). There were 227 FN episodes in 140 children (median age: 6.8 years). 57% of patients had haematological cancer. 12% had bacteraemia and 19% had significant infection.
Target condition/reference standard: Significant bacterial infection, defined as any blood or urine culture positive for bacteria, interstitial or lobar consolidation on chest X-ray or unexpected death from infection (patient was not receiving palliative treatment) before ANC recovery.
Index tests and comparators:

(i) General appearance unwell on first exam versus not (ii) Localised bacterial infection versus not (iii) Maximum temperature >39.0°C versus not
Follow up: Length of follow-up was not reported.
Comments: Patients were admitted to a single institution between 1st August 1996 and 31st July 1997. (i) OR 2.35 (95%CI: 1.17-4.73) (P=0.03) TP=17 FP=40 FN=26 TN=144 (ii) OR 0.47 (95%CI: 1.16-1.35) (P=0.24) TP=4 FP=33 FN=39 TN=151 (iii) OR 2.16 (95%CI: 1.11-4.20) (P=0.04) TP=23 FP=64 FN=20 TN=120

Author(s): Klastersky *et al.* 2000 **Country:** Multinational
Study Design: Prospective study. Consecutive or random sample (depending on participating institution).
Study participants: Adult patients (>16 years) with malignancy treated with chemotherapy and neutropenia (ANC >500/mm^3) and fever (>38.0°C). There were 756 FN episodes in 756 patients (derivation set). Median age was 52 years (range: 16-91). 331/756 (44%) patients had haematological cancer.
Target condition/reference standard: Adverse events, defined as fever resolution for five consecutive days with occurrence of a serious medical complication including death.
Index tests and comparators: (i) Temperature ≥39.0°C versus <39.0°C (ii) Confusion or altered mental state versus not (iii) Symptoms: severe or moribund versus moderate (iv) Symptoms: severe or moribund versus none or mild

Follow up: Follow-up was not reported.
Comments: Patients were registered at 20 institutions (15 countries) between December 1994 and November 1997. (i) OR 2.02 (95%CI: 1.34-3.04) (P<0.001) TP=52 FP=196 FN=61 TN=447 (ii) OR 7.15 (95%CI: 3.56-14.37) (P<0.001) TP=18 FP=17 FN=94 TN=627 (iii) OR 5.77 (95%CI: 3.57-9.31) (P<0.001) TP=56 FP=74 FN=41 TN=304 (iv) OR 13.9 (95%CI: 7.3-26.3) (P<0.001) TP=56 FP=74 FN=14 TN=257

Author(s): West *et al.* 2004 **Country:** United States of America
Study Design: Retrospective observational study.
Study participants: Paediatric patients (<18 years) with treatment induced neutropenia (ANC >500/mm^3 or <1000/mm^3 and falling) and fever (single temperature of ≥38.5°C or at least three temperatures of >38°C an hour apart within 24h). There were 304 FN episodes in 143 patients. Mean age was 7.6 years (±SD 4.6). 57% of patients had a haematological cancer.
Target condition/reference standard: Critical care therapy, defined as fluid resuscitation of ≥60 ml/kg body weight above maintenance fluid requirements, mechanical ventilation or the use of vasoactive infusions.
Index tests and comparators: (i) Presence of chills within 24 hours of presentation versus not (ii) Oral mucositis versus not
Follow up: Not reported
Comments: Patients had presented with febrile neutropenia at a single centre between January 1st 1994 and 31st December 1998. 36/303 episodes required critical care treatment.

(i) OR 2.66 (95%CI: 0.85-8.34) (P=0.10) TP=4 FP=12 FN=32 TN=255

(ii) OR 1.83 (95%CI: 0.90-3.73) (P=0.11) TP=14 FP=69 FN=22 TN=198