Citation: Bjornsson S, Preisler H, Henderson ES. A study of antibiotic therapy in fever of unknown origin in neutropenic cancer patients. Medical & Pediatric Oncology 1977;3(4):379-85.

Design: RCT

Country: USA

Aim: To determine whether neutropenic cancer patients with fever of unknown origin benefits from treatment with broad-spectrum antibiotics for > 3 days.

Inclusion criteria

Patients with:

- temperature 38°C (not judged to be secondary to blood-product transfusions)
- peripheral blood granulocyte count < 500/μl
- no response to antibiotic treatment consisting of carbenicillin (500 mg/kg/day IV), cephalothin (150 mg/kg/day IV) and gentamicin (5 mg/kg/day IV; dosage adjusted to maintain serum levels of 2-8 μg/ml) within days 1-3 of treatment and no focus of infection or likely aetiological organism isolated within these first 3 days of antibiotic treatment
- no exposure to antibiotics during ≥ 2 days immediately preceding onset of fever

Exclusion criteria None reported

Population

Control: N = 6; median age = 45.5 (range = 25-55) years. N = 5 had acute myelocytic leukemia (AML) and N = 1 had lymphoma.

Chloramphenicol/clindamycin: N = 11; median age = 49 (range = 21-66) years. N = 9 had AML and N = 2 had lymphoma. N = 6 received antibiotics + chloramphenicol and N = 5 received antibiotics + clindamycin.

All patients were receiving or had recently finished a course of anti-cancer chemotherapy.

Interventions

After no response and continuous fever of unknown origin after 3 days of treatment with carbenicillin (500 mg/kg/day IV), cephalothin (150 mg/kg/day IV) and gentamicin (5 mg/kg/day IV; dosage adjusted to maintain serum levels of 2-8 μg/ml) the patients were randomised to one of the following 3 groups:

- Control: Stop antibiotic treatment
- Chloramphenicol: Continue with the antibiotic treatment outlined above + chloramphenicol (50 mg/kg/day IV) for an additional 7 days.
- Clindamycin: Continue with the antibiotic treatment outlined above + clindamycin (30 mg/kg/day IV) for an additional 7 days.

Granulocyte transfusions were not given during the first 3 days on study [that is, the 3 days preceding randomisation], but were subsequently given as clinically indicated.

Outcomes See below

Results

Mortality:

- 2 weeks after randomisation 11/11 chloramphenicol/clindamycin patients and 3/6 control patients were still alive (p = .029). Further details of the 3 deaths: Patient 1: Off 3 days, blood grew klebsiella, no remission of AML, died in 1 week, autopsy showed systemic candida and klebsiella in lung. Patient 2: Remained febrile, autopsy showed systemic candida and klebsiella in heartblood. Patient 3: Remained febrile, off 2 days, blood grew klebsiella, urine e. coli., restarted, one blood culture grew candida, no remission [from AML?], died 3 days later (no autopsy).
- 4 weeks after randomisation 9/11 chloramphenicol/clindamycin patients and 3/6 control patients were still alive (p = .21). Further details of the 2 additional deaths: Patient 4: Became afebrile after 5 days, developed pseudomonas pneumonia, no remission of AML, died in 18 days (no autopsy). Patient 5: Remained febrile, no

remission of AML, died in 27 days. WBC transfusions: - Control: 3 patients had no WNC transfusions and 3 patients had 3 WBC transfusions. Chloramphenicol/clindamycin: 4 patients had no WNC transfusions, 4 patients had 1 WBC transfusion and 3 patients had 4 WBC transfusions.
General comments This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis and has a very small sample size. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.
References of Included Studies (For systematic reviews):

Citation: Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. J Pediatr Hematol Oncol 2000 Sep;22(5):405-11.

Design: Randomised, double-blind placebo-controlled trial

Country: Canada

Aim: To determine whether antibiotics can be safely discontinued without an increase in fever recurrence or bacterial infection before neutrophil recovery in paediatric oncology patients at low-risk for bacterial infection who had resolved fever but persistent neutropenia at the time of discharge.

Inclusion criteria

Paediatric oncology patients:
- aged 6 months to 18 years
- admitted to hospital for the management of fever (oral or equivalent temperature >38.5°C once or >38°C on two or more occasions during a 12-hour period) and neutropenia (ANC $<0.5 \times 10^9$/L).
- treated initially with broad-spectrum intravenous antibiotics (piperacillin 50 mg/kg per dose every 6 hours and gentamicin 2.5 mg/kg per dose every 8 hours, or a similar combination. Other antibiotics may have been administered in addition to these if there was a suspicion of a localized infection).
- who continued to have neutropenia between 48 and 120 hours after admission and who were afebrile > 24 hours, had negative blood culture results, and an absence of clinical sepsis (decreased level of consciousness, decreased systolic blood pressure (<5% for age), hypoxemia (oxygen saturation <95%), tachycardia (>90th percentile for age), tachypnea (>90th percentile for age), metabolic acidosis (pH <7.28), or decreased urine output (<0.5 mL/kg per hr for >1 hr) (18).

Enrolled patients were eligible to re-enter the trial if they fulfilled the inclusion and exclusion criteria during subsequent episodes of fever and neutropenia.

Exclusion criteria

- Allergy to penicillin or cephalosporin antibiotics
- bacteremia
- localized infection necessitating antibiotic therapy
- fever > 96 hours after starting intravenous antibiotics
- inability to tolerate oral medications
- underlying cancer not in bone marrow remission
- comorbid conditions necessitating continued inpatient stay.

Population *73 episodes in 54 patients were enrolled in the study.*

Intervention: N = 37 episodes, 43% males; median age = 4.9 years; median discharge ANC ($\times 10^9$/L) = 0.08; median discharge monocyte count ($\times 10^9$/L) = 0.2; median discharge platelet count ($\times 10^9$/L) = 108; bone marrow recovery at discharge = 78%; median peak temperature (°C) = 38.9; median documented neutrophil recovery (days after admission) = 9; concomitant G-CSF therapy = 8%; tumor type acute lymphocytic leukemia (ALL) = 51%, acute myeloid leukemia (AML) = 14%, brain tumour = 11%, non-Hodgkin lymphoma (NHL) = 5%, other = 19%.

Control: N = 36 episodes, 39% males; median age = 4.3 years; median discharge ANC ($\times 10^9$/L) = 0.1; median discharge monocyte count ($\times 10^9$/L) = 0.16; median discharge platelet count ($\times 10^9$/L) = 110; bone marrow recovery at discharge = 75%; median peak temperature (°C) = 39; median documented neutrophil recovery (days after admission) = 9; concomitant G-CSF therapy = 17%; tumor type acute lymphocytic leukemia (ALL) = 58%, acute myeloid leukemia (AML) = 8%, brain tumour = 8%, non-Hodgkin lymphoma (NHL) = 8%, other = 18%.
There were no statistically significant differences between the two treatment arms on the above variables.

Interventions

Intervention: Cloxacillin syrup or capsules 75 to 100 mg/kg per day four times daily, and cefixime syrup 8 mg/kg per day one dose daily. Oral therapy continued until the ANC exceeded 0.5×10^9/L, or until a total of 14 days of intravenous plus oral treatment had been administered.
Control: Appropriate placebos.

Outcomes

Primary: Recurrence of fever or newly documented bacterial infection before neutrophil recovery.
Secondary: Medication side effects, and compliance.

Results

- Recurrent fever: Two episodes (6%; 95% CI 0-13%) in the control group and five episodes (14%; 95% CI 2-25%) in the intervention group were readmitted to hospital with recurrent fever while still neutropenic (p = .43).
One of the readmissions in the control group had positive central and peripheral blood cultures for viridans group streptococci, which responded to a full course of intravenous antibiotics. Cultures in the remaining six readmitted patients were negative. All of the readmissions were uneventful and no deaths occurred during the study period.
- Compliance: Compliance did not differ significantly between the intervention (mean compliance: cefixime = 91%, cloxacillin = 84%) and control groups (mean compliance: cefixime = 90%, cloxacillin = 94%) *Based on patient reported data from 74% of the episodes and a pharmacy-conducted dose count from 87% of the episodes.*
- Side effects: 31% of intervention episodes and 11% of placebo episodes (p = .095). *Based on patient reported data from 74% of the episodes.*
Overall, diarrhoea was the most common side effect (13%), followed by nausea and vomiting (11%), and rash (6%). *Based on patient reported data from 74% of the episodes.*

General comments

In this RCT patients were centrally randomised with stratification for discharge ANC, and if the patients were re-enrolled during a subsequent episode of fever and neutropenia, they were re-stratifified and re-randomised. Blinding of both patient and physician was employed and all variables were recorded blinded to outcome. However, it is unclear which method of randomisation was employed and whether there was adequate allocation concealment, - although central randomisation is likely to have gone some way in ensuring the latter. The study appears to be adequately powered and employed intention to treat analysis. Therefore this study is unlikely to be subject to a high risk of bias and can be regarded as constituting moderate to high quality evidence although for the present purposes there is limited overlap between the reported outcomes and the pre-specified outcomes of interest to the GDG.

References of Included Studies (For systematic reviews):

Citation: Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Levine AS, Deisseroth AB, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. The American journal of medicine 1979;67(2):194-200.
Design: RCT **Country**: USA **Aim**: To evaluate the effectiveness of continuing compared to discontinuing antibiotic treatment after day 7 of antibiotic treatment in patients initially presenting with fever and granulocytopenia who remain granulocytopenic but not febrile on treatment day 7.

Inclusion criteria

Patients of the pediatric oncology branch with:
- fever (either 3 oral temperature elevations above 38°C during 24 hour period or a single temperature elevation ≥ 38.5°C) on day 1
- granulocytopenia (absolute granulocyte count < 500 polymorphonuclear leukocytes and bandforms/mm^3) on day 1
- no documented infection after 7 days of treatment with an empiric antibiotic regimen consisting of Keflin (170 mg/kg/day, IV 4-hourly), gentamicin (6 mg/kg/day, IV 6-hourly) and carbenicillin (500 mg/kg/day, IV 4-hourly) (KGC)
- granulocytopenia (granulocyte count remaining ≤ 500/mm^3) but no fever on day 7 (according to two separate measurements of fever and granulocyte count during the preceding 24 hours)

Exclusion criteria

Patients with
- documented infection
- resolution of both fever and granulocytopenia on day 7
- resolution of granulocytopenia but not of fever on day 7
- fever and granulocytopenia on day 7

Population

Intervention: N = 16; median age = 15 (range 1-30) years; 9 males; underlying malignancy: leukemia (N = 9), lymphoma (N = 2), solid tumour (N = 5); median duration of granulocytopenia = 12 (range 9-25) days.
Control: N = 17; median age = 14 (range 2-33) years; 13 males; underlying malignancy: leukemia (N = 12), lymphoma (N = 1), solid tumour (N = 4); median duration of granulocytopenia = 14 (range 7-25) days.

Interventions

Aminoglycoside levels were determined within 48 hours of initiating antibiotic therapy and adjusted, if required, to maintain a 15 minute post-infusion peak 4-8 µg/ml. None of the patients in this study received oral nonabsorbable antibiotics or was treated in Laminar airflow rooms.
– On day 7 randomisation to either discontinue antibiotics (control group) or to continue receiving antibiotics until granulocytopenia resolved (i.e., polymorphonuclear leukocytes >5OO/mm^3; intervention group).

Outcomes See below

Results

- Intention to treat analysis showed that 7/17 control patients and 1/16 intervention patients became febrile after implementation of randomised interventions (from day 8 onwards; p = .024). [2 control patients were taken off antibiotic treatment on day 8 due to severe hyponatremia and rising liver transaminase – it was 1 of these 2 control patients who subsequently became febrile].
- 2 control and no intervention patients died.
- Non-infectious complications: Electrolyte abnormalities (control: N = 9; intervention = 10), abnormal liver function tests (control: N = 1; intervention = 4), renal abnormalities (serum creatinine 1.5-3 mg/dl; control: N = 1; intervention = 1), yeast colonisation (control: N = 3; intervention = 5), phlebitis (control: N = 1; intervention = 1), rash (control: N = 1; intervention = 1).

General comments

This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.

References of Included Studies (For systematic reviews):

Citation: Santolaya ME, Villarroel M, Avendano LF, Cofre J. Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis 1997 Jul;25(1):92-7.

Design: RCT
Country: Chile
Aim: To examine the safety of stopping antibiotic therapy on day 3 of treatment in children with cancer, non-

bacterial fever and neutropenia.

Inclusion criteria

Children hospitalised because of a cancer, fever, and severe neutropenia (ANC ≤ 500/mm^3) with no identifiable focus of bacterial infection, hemodynamic stability, negative admission cultures, and serum CRP levels of ≤ 40 mg/L on days 1 and 2.

Exclusion criteria

Children who had clinical and/or laboratory evidence of bacterial infection and/or a serum CRP level of > 40 mg/L on day 1 or 2 as they were considered potentially bacteremic.
It is not mentioned as an exclusion criterion, but 14 patients were excluded because antimicrobial treatment was administered during the 7 days before admission.

Population *75 episodes in 68 patients were enrolled in the study.*

Intervention: N = 39; mean age = 5.6 (SD = 3.8) years; 21 males; oncological disease: leukemia (N = 18), lymphoma (N = 1), solid tumour (N =20); chemotherapy status: Induction (N = 28), maintenance (N = 11); indwelling catheter (N = 17); mean ANC (/mm^3) on day 1 = 246 (SD = 167).
Control: N = 36; mean age = 6.8 (SD = 4.3) years; 20 males; oncological disease: leukemia (N = 15), lymphoma (N = 2), solid tumour (N =19); chemotherapy status: Induction (N = 27), maintenance (N = 9); indwelling catheter (N = 13); mean ANC (/mm^3) on day 1 = 297 (SD = 181).
There were no statistically significant differences between the two treatment arms on the above variables.

Interventions

Therapy with an antistaphylococcal penicillin and a third-generation cephalosporin or an aminoglycoside was started at admission for all children. On day 3 the children were randomised to one of the following two groups:
Intervention: Antibiotic therapy continued until resolution of the episode of neutropenia and fever.
Control: All antibiotic therapy stopped.
Trimethoprim-sulfamethoxazole prophylaxis was not administered to any of the patients and no child received treatment with colony-stimulating factors.

Outcomes

Detection of clinical focus suggestive of bacterial infection, positive bacterial culture after day 3, reappearance of fever, deterioration of haemodynamic stability not attributable to blood loss, progressive increase in serum CRP levels to > 40mg/L during ≥ 2 consecutive measurements. All these outcomes were considered unfavourable and indicators of restarting antibiotics in the control group and adjusting antibiotic therapy in the intervention group. Outcomes were considered favourable when none of these (unfavourable) variables occurred.

Results

- Mean duration of fever = 2.7 (SD = 1.82) days in the control group and 3.5 (SD = 3.62) days in the intervention group (ns).
- Mean duration of severe neutropenia = 8.3 (SD = 5.42) days in the control group and 9 (SD = 5.83) days in the intervention group (ns).
- Mean hospital stay = 8 (SD = 5.22) days in the control group and 9 (SD = 5.87) days in the intervention group (ns).
- Favourable outcomes occurred in 34/36 control episodes and in 36/39 intervention episodes.
- Antibiotic therapy was stopped in 29 febrile episodes that resolved and in 7 febrile episodes despite continuous fever in the control group.
- Mean duration of antibiotic treatment = 7 (SD = 3.98) days in the intervention group.
- No deaths occurred.
- Discharge diagnoses: adenovirus infection (control: N = 4; Intervention: N = 3), respiratory syncytial virus infection (control: N = 3; Intervention: N = 6), parainfluenza virus infection (control: N = 3; Intervention: N = 3), influenza virus infection (control: N = 0; Intervention: N = 1), clinical upper respiratory tract infection (control: N = 7; Intervention: N = 5), varicella (control: N = 6; Intervention: N = 8), hepatitis A (control: N = 0; Intervention: N = 1), enterovirus infection (control: N = 1; Intervention: N = 1), mixed infection (control: N = 2; Intervention: N = 1), coagulase-negative staphylococcus infection (control: N = 0; Intervention: N = 2), fever of unknown origin (control: N = 10; Intervention: N = 8).

General comments This RCT was not placebo-controlled and reports no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis. It is therefore unclear which likely degree of bias the study is subject to and the evidence can therefore only be considered of low quality.
References of Included Studies (For systematic reviews): NA