Author(s): Pizzo *et al.* (1982).

Country: United States of America

Study Design: Randomised controlled trial (RCT)

Study participants: Two hundred and seventy-one young patients were treated for six hundred and fifty-two episodes of neutropenic fever. Fifty patients, who still had an undefined infectious aetiology and whose fever and granulocytopenia had not resolved after seven days of treatment with primary empiric antibiotics, were randomised into three treatment groups.

[Group 1] Median age: 15 years (range: 2-22 years). Ratio of male: female=10:6; Leukemia (N=5); Lymphoma (N=3); Solid tumour (N=8). Yeast colonisation of GI tract (N=14).

[Group 2] Median age: 16 years (range: 2-25 years). Ratio of male: female=8:8; Leukemia (N=8); Lymphoma (N=3); Solid tumour (N=5). Yeast colonisation of GI tract (N=13).

[Group 3] Median age: 18 years (range: 8-30 years). Ratio of male: female=14:4; Leukemia (N=9); Lymphoma (N=3); Solid tumour (N=6). Yeast colonisation of GI tract (N=14).

The three randomisation groups were said to be similar in all respects at baseline but no supporting statistics were offered.

Interventions and comparators:

[Group 1] (N=16) Discontinue the empiric antibiotic (Keflin® at 170mg kg^{-1} day^{-1} iv every 4h with gentamicin at 6mg kg^{-1} day^{-1} iv every 6h and carbenicillin at 500mg kg^{-1} day^{-1} iv every 4 h (KGC))*.

[Group 2] (N=16) Remain on the empiric primary antibiotic (KGC) until the resolution of fever and granulocytopenia (granulocytes >500 per µl measured twice 24h apart).

[Group 3] (N=18) Continue the empiric antibiotic (KGC) adding amphotericin B (0.5mg kg^{-1} day^{-1} iv every 24h) until the resolution of fever and granulocytopenia (granulocytes >500 per µl measured twice 24h apart).

*Patients in Group [1] resumed treatment if a clinical or microbiological source of infection was identified or if their systolic BP <80mm Hg with fever and clinical deterioration.

Outcomes: Clinical response.

Results:

Infectious complications:

[Group 1] 9/16 (56%) patients in this group experienced infectious complications a median of three days post randomisation. Six patients had a systolic BP <80mm Hg, three of whom had positive blood cultures showing micro-organisms responsive to the discontinued KGC and three patients who had negative blood cultures but responded to anti-hypotensive therapy and the reinstitution of KGC. The three other patients did not have hypotension but experienced complications associated with infection: retropharyngeal abscess, scrotal cellulitis and oesophageal candidiasis.

The first two of these patients responded to the reinstitution of antibiotics and the third to the anti-fungal therapy.

[Group 2] 6/16 (37.5%) patients who continued antibiotic therapy developed an infectious complication which occurred at a median of 8 days after randomisation. Five of these six infections were fungal and the other bacterial (*E. Coli* resistant to KGC). Two of the patients with fungal infections subsequently died whilst the other three had infections that responded to systemic amphotericin B. One additional patient died of GI haemorrhage (due to disseminated candidiasis) three days after stopping anti-fungal treatment, taken for 16 days until fever resolution.

[Group 3] 2/18 (11%) patients who received antibiotic and anti-fungal therapy experienced infectious complications. One of these patients died of disseminated cytomegalovirus after 30 days of persistent fever and neutropenia. The second patient died of severe pulmonary haemorrhage after 42 days due to invasion of the lung, via the bronchial artery, by a fungal organism resistant to amphotericin B.

The incidence of infectious complications for patients who continued KGC plus amphotericin B [Group 3] was significantly less than for patients who discontinued antibiotic therapy [Group 1] (P=0.013) but not from patients who remained on KGC [Group 2] (no P value).

The incidence of shock (6/16 patients) in Group 1, following antibiotic discontinuation, was significantly greater than patients in either Group [2] (N=0) or [3] (N=0) (P<0.02 per comparison or P<0.001 across three groups).

Time to initial defervescence after randomisation also differed betweens groups: median 6 days (range: 2-20 days) [Group 3] versus median 8 days (range: 3-23 days) [Group 2] versus median 11 days (range: 3-22 days) [Group 1]. Given the wide ranges and low patients numbers, there would be unlikely to be a significant difference between groups for this outcome but no statistics were presented.

Time to defervescence and resolution of granulocytopenia was: median 14 days (range: 4-44 days) [Group 3] versus median 10 days (range: 4-34 days) [Group 2] versus median 21 days (range: 4-42 days) [Group 1]. Given the wide ranges and low patients numbers, there would be unlikely to be a significant difference between groups for this outcome but no statistics were presented.

Non-infectious complications:

The number of non-infectious complications did not differ significantly between the three groups. The median duration of granulocytopenia was 24 days with no significant difference between the three treatment groups.

[Group 1] Electrolyte abnormalities (N=16) hepatic enzyme elevations (N=1) phlebitis (N=1).

[Group 2] Electrolyte abnormalities (N=16) hepatic enzyme elevations (N=3) rash (N=1) phlebitis (N=1).

[Group 3] Electrolyte abnormalities (N=18) hepatic enzyme elevations (N=2) azotemia (N=1) phlebitis (N=1).

Death:

[Group 1] Infectious (N=2) non-infectious (N=3) [Group 2] Infectious (N=3) non-infectious (N=2) [Group 3] Infectious (N=2) non-infectious (N=1)
Comments: This paper presented data from a randomised comparison of empiric anti-fungal therapy administered to patients with neutropenia who were febrile after seven days of empiric primary antibiotics. These patients were divided into two populations: those with unexplained fever and those with a documented infection. The results for the first group are further described here. Fever was defined as three temperature elevations above 38°C during a 24-hour period or a single elevation of 38.5°C. Granulocytopenia was defined as an absolute count of <500 per µl of polymorphonuclear leucocytes and band forms. Given their results, the authors suggested that the continuation of antibiotic therapy [Group 2] may have decreased the incidence of hypotension and early bacterial infection but increased the incidence of serious fungal infection. They pointed out that two deaths from infection in Group 1 were due to bacteria that were sensitive to the KGC regime, which had been discontinued, whilst two deaths in Group 2 were due to invasive fungal infections which might have been prevented by earlier administration of anti-fungal therapy. They considered that the combined therapy appeared to be beneficial in children and young patients who, after seven days of empiric antibiotics, remained febrile, regardless of whether or not a focus of infection was initially identified. Although this low number study was reported as a randomised comparison, there were no methodological details provided, including randomisation or allocation, and very limited statistical analysis which rendered it of very low evidential quality.

Author(s): EORTC International Antimicrobial Therapy Cooperative Group (1989). **Country:** Various
Study Design: Data from two **r**andomised controlled trials (RCT)
Study participants: One hundred and fifty-seven patients, from two RCTs. After four days of empiric antibiotics, patients with persistent severe granulocytopenia and fever without microbiologically documented pathogens but with clinical infection (known or likely) were randomised into two groups. [Group 1] Mean age: 38.5 years (range: 4-78 years) Ratio of male: female = 43:25. Leukemia (N=49); Solid tumours (N=6); Other (N=13). Previous anti-fungal prophylaxis (N=31). [Group 2] Mean age: 40.1 years (range: 1-81 years) Ratio of male: female = 37:27. Leukemia (N=50); Solid tumours (N=5); Other (N=9). Previous anti-fungal prophylaxis (N=39).
Interventions and comparators: [Group 1] (N=68) Empiric antibiotics, including azlocillin, cefotaxime, ticarcillin, amikacin and

ceftazidime (unknown schedule) plus amphotericin B (0.6mg kg^{-1} day^{-1} iv every 24h or 1.2mg kg^{-1} day^{-1} iv every 48h). Anti-fungal treatment was continued until bone marrow recovery.

[Group 2] (N=64) Empiric antibiotics only.

Protocol violations occurred in 12 Group 1 patients (for not receiving amphotericin B) and in 13 Group 2 patients (for receiving amphotericin B before day 9), leaving 132 evaluable. Amphotericin B was administered in Group 2 if a fungal infection was documented, or if a patient remained febrile 5 days after randomisation.

Outcomes: Clinical response. The response rate was calculated by assessing treatment as a failure if a patient remained febrile five days after randomisation.

Results:

More (31/45) patients in Group 1 had profound granulocytopenia at randomisation (69% univariate) than patients in Group 2 (20/43, 46% univariate) (P=0.06).

Overall response rate:

47/68 (69%) of all patients in Group 1 versus 34/64 (53%) of all patients in Group 2 were considered to have had treatment success (P=0.09).

38/57 (67%) of patients >15 years in Group 1 versus 24/51 (47%) of patients >15 years in Group 1 were considered to have had treatment success (P=0.06).

21/27 (78%) patients in Group 1 (i.e. given Amphotericin B) that had not received prior anti-fungal prophylaxis, experienced a higher treatment success rate than the 9/20 (45%) patients in Group 2 (i.e. given antibiotics only) that had also not received prior anti-fungal prophylaxis (P=0.04). Patients in both groups who had received anti-fungal prophylaxis experienced equal treatment success rates (19/31) (61%) in Group 1 versus 24/39 (61%) in Group 2.

For 22/29 (75%) patients in Group 1 with a clinically documented infection assessed at day 4, treatment was more effective than for 14/31 (41%) similar patients in Group 2 (P=0.03). There was no correlation between Amphotericin B dose and clinical response. In multivariate analysis, it was shown that age (less or more than 15 years) and previous anti-fungal prophylaxis (yes or no) were the two important prognostic factors. The treatment effect remained significant after adjustment for these two factors.

Six patients in Group 1 discontinued empiric Amphotericin B due to immediate side effects including chills, allergic reactions or infusion related high fever, or a combination of the three.

Overall survival:

There was one documented case of fungal infection in Group 1 patients, versus six cases in Group 2 (including two fatalities due to invasive candidiasis, one from a pulmonary *Aspergillus* infection and one from disseminated *Mucor*) (P=0.05 between groups). The incidence of nephrotoxicity was no higher in Group 1 (8/68 (11%)) compared with Group 2 (3/64 (4%)) but hypokalemia occurred significantly more frequently in Group 1 (33/68 (48%)) than Group 2 (16/64 (25%)) (P=0.009).

Eleven patients in Group 1 had died by day 30 versus 14 in Group 2 (P=0.039). One death was

due to a pulmonary infection of undiagnosed aetiology and one from an unspecified bacterial infection. The remaining deaths were described as being due to 'other causes'. Similarly in Group 2, there were two deaths due to unspecified bacterial infections and eight from 'other causes'.
Comments: This paper presented data from patients that had been randomised into two large, multi-centre EORTC trials comparing various antibiotic regimens in patients with granulocytopenia and fever. After four days of persistent fever, patients were randomised to continue taking their primary empiric antibiotics with or without the addition of Amphotericin B. Fever was defined as a temperature elevation above 38°C. Severe granulocytopenia was defined as an absolute count of <500 per µl of polymorphonuclear leucocytes. The original studies may well have been conducted with rigor but there are no details of randomisation in this follow-on work, although the statistical methodology appears to be sound. There is very little detail about the incidence or identity of bacterial infections in either group.

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

Country: Multinational

Study Design: Randomised controlled trial

Study participants: Seven hundred and sixty-three eligible patients were enrolled on this study. After 48-60 hours of empiric antibiotics, one hundred and sixty-five patients with neutropenia and persistent fever, either of unknown cause, clinically documented infection or microbiologically documented infection with a Gram +ve organism, were randomised into two groups.

[Group 1] Mean age: 42 years (range: 4-76 years) Adults: 81/86 (94%) Leukemia (N=53); Lymphoma or Hodgkin disease (N=31); Other (N=2). Gram +ve bacteremia (N=10); Clinically documented infection (N=14) Fever of unknown origin (N=62).

[Group 2] Mean age: 42 years (range: 4-78 years) Adults: 75/79 (95%) Leukemia (N=48); Lymphoma or Hodgkin disease (N=26); Other (N=5). Gram +ve bacteremia (N=8); Clinically documented infection (N=13) Fever of unknown origin (N=58).

Exclusions: Age <2 years; a known allergy to any of the protocol drugs; previously included in the study; having received an iv antibiotic within 4 days of study initiation; likelihood of death in the following two days; renal failure; poor creatinine clearance; catheter related infection; known HIV infection; pregnant or with a lung filtrate.

Interventions and comparators:

[Group 1] (N=86) Empiric antibiotic: Piperacillin-tazobactam (P-T) at 4.5g every 6 hours iv (less for smaller children) plus vancomycin at 15mg kg^{-1} every 12 hours (max daily dose of 2g).

[Group 2] (N=79) Empiric antibiotic plus placebo (saccharose solution).

Patients were treated until resolution of fever and/or infection for a minimum of four consecutive

days. After that, patients with persistent fever were treated at the discretion of the clinician.

Outcomes: Time to defervescence, defined as a period of three days with a temperature of <38°C and the numbers of patients in each arm who had resolution of fever. All other clinical outcomes.

Results:

Fever resolution:

82/86 (95%) of Group 1 patients experienced fever resolution versus 73/79 (92%) of Group 2 patients (P=0.52).

Therapy was not modified in 42/86 (49%) of Group 1 patients or 36/79 (46%) of patients in Group 2. The most frequent modification was the addition of a glycopeptide to vancomycin and the stopping of the placebo for patients who then received vancomycin or teicoplanin. 31/86 (36%) of patients in Group 1 and 30/79 (38%) of patients in Group 2 received amphotericin B.

Median time to defervescence overall was 3.5 days (95%CI: 2.7-4.4) in Group 1 versus a median of 4.3 days (95%CI: 3.5-5.1) in Group 2 (P=0.75). HR: 1.03 (95%CI: 0.75-1.43).

Median time to defervescence for those patients who received the allotted regimen for the four days was 3.1 days (95%CI: 2.3-4.0) in Group 1 (N=76) versus a median of 4.0 days (95%CI: 3.3-4.7) in Group 2 (N=66) (P=0.91).

Mortality:

[Group 1] 4/86 patients (5%) died between days 14 and 31 after study entry. Deaths were due to: Gram –ve infection (N=1); extensive cancer (N=2) and haemorrhage (N=1).

[Group 2] 8/79 patients (10%) died between days 7 and 35 after study entry. Deaths were due to: Gram –ve infection (N=2); diffuse peritonitis (N=1); haemorrhage (N=3) and extensive cancer (N=3)

Adverse events:

[Group 1] 9/86 (10%) patients experienced adverse treatment-related events: rash (N=3); pruritis (N=2); nephrotoxicity (N=2); swelling of the lips (N=1) and red man syndrome (N=1).

[Group 2] 3/79 (4%) patients experienced adverse treatment-related events: colitis (N=1); diarrhoea (N=1) and rash (N=1).

Comments: This paper describes the results of randomised controlled trial for which 859 patients were enrolled between December 1997 and June 2000 at 34 centres throughout Europe, the Middle East and North America. The aim was to determine the effect of the addition of a Gram +ve antibiotic to empiric broad spectrum antibiotics given to cancer patients with unresolved neutropenia and fever.

Granulocytopenia was defined as an absolute granulocyte count ≤1,000 cell mm-3 which was expected to fall to <500 cells mm^{-3} within 24-48 hours and remain at that level for >7 days after the onset of fever. Fever was defined as an oral or axillary temperature of ≥38.5°C once or >38°C

on ≥2 occasions at least one hour apart within a 12 hour period.

The study was designed to detect an improvement in the time to defervescence of 36 hours in the intervention group from 96 hours to defervescence in the placebo group. The sample size should have been 113 patients in each arm for 85% power but, clearly, the numbers fell well short (the trial was closed early for this reason) and hence the trial was underpowered.

The authors concluded that, despite the underpowering of their study, the addition of vancomycin to the empiric antibiotic regime did not appear to be justified.

Author(s): Erjavec *et al.* (2000)

Country: The Netherlands

Study Design: Randomised controlled trial (RCT)

Study participants: One hundred and fifteen eligible adult patients were enrolled on this study. After 72-96 hours of empiric antibiotics, one hundred and fourteen patients with neutropenia and persistent fever, either of unknown cause, clinically documented infection or microbiologically documented infection with a Gram +ve organism, were randomised into two groups.

[Group 1] Mean age: 50.7 years (SD: 13.9 years) Adults: 81/86 (94%) Ratio of male: female = 28:28; Leukemia (N=32); Non-Hodgkin's lymphoma (N=9); Autologous stem cell transplant (N=12); Other (N=3). Antibacterial prophylaxis (N=51); Clinically documented infection (N=13) Fever of unknown origin (N=28).

[Group 2] Mean age: 42 years (range: 4-78 years) Adults: 75/79 (95%) Ratio of male: female = 35:23; Leukemia (N=37); Non-Hodgkin's lymphoma (N=9); Autologous stem cell transplant (N=10); Other (N=2). Antibacterial prophylaxis (N=52); Clinically documented infection (N=11) Fever of unknown origin (N=32).

Exclusions: identification of micro-organisms known to be resistant to protocol drugs; suspicion of fungal infection; signs or symptoms of a central line infection; clinical deterioration; known allergy to protocol drugs; renal failure; severe cardiac, hepatic or neurological disease.

Interventions and comparators:

[Group 1] (N=56) Empiric antibiotic: Imipenem at 500mg four times daily iv. plus teicoplanin at 400mg per 24h.

[Group 2] (N=58) Empiric antibiotic plus placebo.

Assigned treatments were given twice on the first day of randomisation and, for patients with a positive response, for five afebrile days thereafter. After 72 hours, non-responders in the placebo group were treated with teicoplanin and anti-fungal or anti-viral drugs as indicated (open label).

Outcomes: Survival, cause of death, time to fever resolution.

Results:

Fever resolution:

[Group 1] Response within 72 hours: 25/56 (45%) patients. Bone marrow regeneration was assumed in 9 patients amongst the responders.

[Group 2] Response within 72 hours: 27/58 (47%) patients. Bone marrow regeneration was assumed in 7 patients amongst the responders.

The lack of response was, in the majority of patients, for an unknown reason.

Survival:

[Group 1] Death whilst aplastic: 6/56 (11%)

[Group 2] Death whilst aplastic: 4/58 (7%)

Four patients died from a fungal infection in the teicoplanin arm, three of which were from a superinfection [Group 1] compared with a similar death in Group 2. Other causes of death in Group 1 included septicaemia and respiratory distress syndrome. In the placebo arm, one patient died from tumour progression and two from unrelated cardiac events.

Micro-organisms were isolated as follows: 13 Gram +ve, 2 Gram -ve and 5 non-bacterial organisms in Group 1 compared with 9 Gram +ve, 2 Gram -ve and 5 non-bacterial organisms in Group 2.

Comments:

Neutropenia was defined as an absolute neutrophil count ≤1,000 cell mm^{-3} which was expected to fall with chemotherapy or <500 cells mm^{-3}. Fever was defined as an axillary temperature of >38°C once or >38°C for 24 hours. Persistent fever was defined as a temperature at least 38°C on two consecutive readings 4-8 hours apart.

The trial was 85% powered to detect a 28% significant ($P<0.05$) difference in survival between study arms. Details of randomisation were unsatisfactory (defined as 'computer-assisted') and there were no details of allocation. There was no indication of blinding from the point of view of the administration of placebo and teicoplanin but investigators were apparently blinded in some analyses.

Many of the patients had received anti-bacterial prophylaxis and some had G-CSF. There were no statistical analyses presented, although the authors stated that patient outcomes had been analysed with X^2 testing. Despite any shortcomings, the authors concluded that they 'strongly advocated' the omission of empirical glycopeptides. They found no difference between study arms in the number of patients who became afebrile by three days after randomisation.