1. de Pauw, B. E., Novakova, I. R., & Donnelly, J. P. (1990). Options and limitations of teicoplanin in febrile granulocytopenic patients. *British Journal of Haematology, 76,* Suppl-5.
Country: The Netherlands
Design: Randomised Controlled Trial
Population: 120 febrile granulocytopenic patients with haematological malignancies *unclear how many patients had central lines*
Inclusion criteria: • Age > 14 years • Fever (single anxillary temperature ≥ 38.5°C or two or more readings of > 38°C taken 2-4 hours apart) • Granulocytopenic (<$1.0x10^9$/l expected to fall to <$0.5x10^9$/l)
Exclusion criteria: • No evidence of lung infiltration, skin or soft tissue infection or other obvious focus of infection at fever onset • No other parenteral antibiotics before starting therapy
Interventions: • Ceftazidime 2g 8 hourly as a short infusion Versus

- Ceftazidime 2g 8 hourly as a short infusion with teicoplanin administered as an IV bolus at 800mg in two divided doses on the first day and 400mg once daily thereafter.

Outcomes:

- Death (before or after therapy modification)
- Toxicity
- Clinical response (patient survived the infection and all infectious symptoms disappeared without any change of initial therapy.
- Clinical response after therapy modification (patient survived infection but defervescence and disappearance of all infectious symptoms was achieved only after modification of the empiric regimen

Results:

Death
Ceftazidime - 6/51 (12%)
Ceftazidime + teicoplanin - 4/52 (8%)

Toxicity

Reversible rise of 50-100% in serum creatinine
Ceftazidime - 2/51 (4%)
Ceftazidime + teicoplanin - 2/52 (4%)

Greater than 3-fold rise in alkaline phosphatise and/or transaminases
Ceftazidime - 1/51 (2%)
Ceftazidime + teicoplanin - 5/52 (10%)

Clinical response
Ceftazidime - 25/51 (49%)
Ceftazidime + teicoplanin - 33/52 (63%)

Clinical response after therapy modification
Ceftazidime -20 /51 (39%)
Ceftazidime + teicoplanin -15/52 (29%)

Skin rash
Ceftazidime - 0 /51 (0%)
Ceftazidime + teicoplanin - 8/52 (15%)

Critical care
Not reported

Length of stay

Not reported

Line preservation / "catheter remains in situ"
Not reported

Antibiotic resistance
Not reported

Proven Bacteraemia
Not reported

General comments:

- Three studies by the same research group were reported in this paper. Only study 2 met the criteria set out by the PICO. This was an RCT comparing the efficacy and toxicity of ceftazidime given with and without teicoplanin.
- It was unclear how many patients had central lines.
- There was adequate sequence generation and allocation concealment. Analyses were conducted on an Intention to Treat (ITT) basis.
- The study was not blinded.

2. Del Favero, A., Menichetti, F., Guerciolini, R., Bucaneve, G., Baldelli, F., Aversa, F. et al. (1987). Prospective randomized clinical trial of teicoplanin for empiric combined antibiotic therapy in febrile, granulocytopenic acute leukemia patients. Antimicrobial Agents & Chemotherapy, 31, 1126-1129.
Country: Italy
Design: Randomised Controlled Trial
Population: 66 febrile granulocytopenic episodes in 54 patients with haematological malignancies (age range 8-71 years) *unclear how many patients had central lines*
Inclusion criteria: • Fever (anxillary temperature ≥ 38°C in the absence of obvious non-infective causes) • Granulocytopenic (absolute granulocyte count below 1000/mm^3)
Exclusion criteria: • History of allergy to any antibiotics used in the study • Creatinine level in serum above 2mg/100ml
Interventions:

- Amikacin (15mg/kg per day in 3 equal doses subsequently adjusted to maintain optimal peak (15 to 25 mg/litre) and trough (5mg/litre) levels in serum and ceftazidime 90mg/kg per day in 3 equal doses (each dissolved in 100ml of 0.9% saline and administered intravenously over 15 to 30 min)

Versus

- Amikacin (15mg/kg per day in 3 equal doses subsequently adjusted to maintain optimal peak (15 to 25 mg/litre) and trough (5mg/litre) levels in serum and ceftazidime 90mg/kg per day in 3 equal doses (each dissolved in 100ml of 0.9% saline and administered intravenously over 15 to 30 min) plus teicoplanin 5mg/kg per day in a single dosedissolved in 10ml of sterile water and administered intravenously in 3min with an initial loading dose of 8mg/kg (maximum initial dose 600mg)

Outcomes:

- Response to therapy
- Toxicity

Results:

Death
Not reported

Toxicity
Nephrotoxicity (defined as increase in creatinine in serum of more than 0.4mg/100mlfrom baseline when other causes excluded)
Ceftazidime + amikacin - 0/22 (0%)
Ceftazidime + amikacin + teicoplanin - 0/25 (0%)

Proven Bacteraemia
Ceftazidime + amikacin - 14/22 (64%)
Ceftazidime + amikacin + teicoplanin - 9/25 (36%)

Treatment failure (treatment modification considered a failure)
Ceftazidime + amikacin - 14/25 (56%)
Ceftazidime + amikacin + teicoplanin -18/22 (82%)
(difference not statistically significant P = 0.1)

Critical care
Not reported

Length of stay
Not reported

Line preservation / “catheter remains in situ”
Not reported

Antibiotic resistance

Not reported
General comments: • Sequence generation was adequate, but it is unclear whether concealment was sufficient • The study was not blinded • 29% of episodes were excluded from the analyses. ITT analyses were not conducted. • Patients who showed greatest advantage from the teicoplanin regimen were those with profound (<100/mm^3) and persistent neutropenia (83% improvement in the group with teicoplanin vs. 30% in the group without teicoplanin)

3. **EORTC (1991). Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group.** ***Journal of Infectious Diseases, 163,*** **951-958.**
Country: Canada
Design: Randomised Controlled Trial
Population: 747 febrile granulocytopenic patients with cancer recruited 1986 and 1989 *unclear how many had central lines*
Inclusion criteria: • Granulocytopenia (<1000 cells/mm^3) • Fever (≥ 38°C on one occasion)
Exclusion criteria: • Non-infectious cause of fever • Parenteral antibiotics for ≥ 4 days • Allergic to any of trial antibiotics • Serum creatinine > µmol/l
Interventions: • Ceftazidime plus amikacin Versus • Ceftazidime plus amikacin plus vancomycin
Outcomes: • Treatment success/failure • Death

- Superinfection
- Toxicity

Results:

Death (all cause)
Ceftazidime + amikacin – 19/370 (5%)
Ceftazidime + amikacin + vancomycin – 22/383 (6%)

Super-infection
Ceftazidime + amikacin – 28/370 (8%)
Ceftazidime + amikacin + vancomycin – 22/383 (6%)

Treatment failure (treatment modification considered a failure)
Ceftazidime + amikacin – 138/370 (37%)
Ceftazidime + amikacin + vancomycin – 89/383 (23%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Toxicity
Nephrotoxicity
Ceftazidime + amikacin – 9/370 (2%)
Ceftazidime + amikacin + vancomycin – 24/383 (6%)

Hepatic toxicity
Ceftazidime + amikacin – 50/370 (13.5%)
Ceftazidime + amikacin + vancomycin – 85/383 (22%)

Hypokalaemia
Ceftazidime + amikacin – 35/370 (9%)
Ceftazidime + amikacin + vancomycin – 55/383 (14%)

Ototoxicity
Ceftazidime + amikacin – 1%
Ceftazidime + amikacin + vancomycin – 1%

Coagulation defects
Ceftazidime + amikacin – 2%
Ceftazidime + amikacin + vancomycin – 3%

Diarrhoea

Ceftazidime + amikacin – 2% Ceftazidime + amikacin + vancomycin – 2% <u>Drug fever</u> Ceftazidime + amikacin – 1% Ceftazidime + amikacin + vancomycin – 2%
General comments: • A large sample size relative to the other included studies • Unblinded • Sequence generation was adequate, but the method of concealment was unclear • No ITT analysis

4. Karp, J. E., Dick, J. D., Angelopulos, C., Charache, P., Green, L., Burke, P. J. et al. (1986). Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *American Journal of Medicine, 81,* 237-242.
Country: USA
Design: Randomised Controlled Trial (RCT)
Population: 60 adult patients admitted to a leukaemia service from February 1983 to June 1984 *all had central lines*
Inclusion criteria: • Diagnosis of acute leukaemia • Received intensive timed sequential therapy and augmentation therapy during early complete remission, or chemotherapy alone with fractioned total body irradiation followed by analogous bone marrow rescue transplantation • Fever • Granylocytopenia
Exclusion criteria: • Documented allergy to vancomycin or other routinely used antibiotics • Antibiotics within 7 days of admission
Interventions: • Vancomycin 500mg every 6 hours plus gentamicin 2mg/kg every 6 hours and ticarcillin 45mg/kg every 4 hours Versus • Placebo every 6 hours plus gentamicin 2mg/kg every 6 hours and ticarcillin 45mg/kg every 4 hours

All antibiotics were administered intravenously

Outcomes:

Days of fever
Superinfections

Results:

Death
Not reported (stated that there was no significant difference between groups)

Super-infections
Gentamicin + ticarcillin - 16/29 (55%)
Gentamicin + ticarcillin + vancomycin - 0/31 (0%)

Duration of fever
Gentamicin + ticarcillin - Median - 15.1 days (range 4-40)
Gentamicin + ticarcillin + vancomycin - Median - 10.3 days (range 9-35)

Toxicity
Not reported (stated that there was no added toxicity in vancomycin group

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Antibiotic resistance
Not reported

General comments:

- Sequence generation and allocation concealment were adequate
- Double blinded
- 8% of episodes were excluded from analyses
- Deaths not reported

5. Marie, J. P., Pico, J., Lapierre, V., Maulard, C., Pappo, M., Chiche, D. et al. (1991). Comparative trial of ceftazidime alone, ceftazidime + amikacin and ceftazidime + vancomycin as empiric therapy of febrile cancer patients with induced prolonged neutropenia. *Medecine et Maladies Infectieuses, 21,* 386-388.
Country: France
Design: Randomised Controlled Trial
Population: 223 episodes of febrile neutropenia in 205 patients between October 1987 and June 1989 *unclear how many patients had central lines*
Inclusion criteria: • Underlying neoplastic disease • ≥ 18 years old • Neutropenia (neutrophil count of <500/mm^3 or ≤ 1000/mm^3 and falling) • Fever (oral temperature of ≥38°C on two occasions 6h apart or ≥38.5°C on one occasion not associated with blood product transfusions)
Exclusion criteria: • Parenteral antibiotics in the preceding 96 hours • Known allergy to any of the study drugs
Interventions:

- Ceftazidime (2g intravenously every 8 hours)

Versus

- Ceftazidime (2g intravenously every 8 hours) plus vancomycin (1g every 12 hours)

Vancomycin was added to the ceftazidime arm when fever persisted for more than 96 hours

Outcomes:

- Superinfection
- Tolerance

Results:

Death (all cause)
Not reported

Super-infection

Ceftazidime + vancomycin - 20/77 (26%)
Ceftazidime - 5/77 (6%)

Treatment failure (treatment modification considered a failure)

Ceftazidime + vancomycin - 53/77 (69%)
Ceftazidime - 67/77 (87%)

Tolerance
Skin rash
Ceftazidime + vancomycin - 4/77 (5%)
Ceftazidime - 4/77 (5%)

Renal problems
Ceftazidime + vancomycin - 5/77 (6%)
Ceftazidime - 4/77 (5%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

Toxicity
Tolerance reported (see above)

General comments:

- This paper was published in French
- Sequence generation and concealment were unclear
- The study was not blinded

6. **Molina, F., Pedro, L., Rosell, R., Barnadas, A., Font, A., & Maurel, J. (1993). Randomized open and prospective study of two antibiotic schedules (with and without teicoplanin) for post-chemotherapy episodes of neutropenic fever.** ***Oncologia: IV Congresso Nacional de la SEOM, 16,*** **247.**
Country: Spain
Design: Randomised Controlled Trial
Population: Number randomised unknown. 36 were evaluated. *unclear how many patients had central lines*
Inclusion criteria: • Unclear (awaiting paper)
Exclusion criteria: • Unclear (awaiting paper)
Interventions: • Unclear (awaiting paper)
Outcomes: • Unclear (awaiting paper)
Results: <u>Death (all cause mortality)</u>

Awaiting paper...
General comments: • Unclear whether methods of sequence generation and allocation concealment were adequate • Study was not blinded • (awaiting paper)

7. Novakova, I., Donnelly, J. P., & de Pauw, B. (1991). Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. Antimicrobial Agents and Chemotherapy, 35, 672-678.
Country: The Netherlands
Design: Randomised Controlled Trial
Population: 120 febrile granulocytopenic patients with haematological or solid tumours *unclear how many patients had central lines*
Inclusion criteria: • >14 years of age • Granulocytopenic (granulocyte counts expected to fall to < 0.5 x 10^9/litre) • Febrile (single anxillary temperature ≥ 38.5°C or at least 2 readings of > 38°C taken 2 to 4 hours apart) • No obvious focus of infection
Exclusion criteria: • Infective focus (such as a lung infiltrate) at the onset of fever
Interventions: • Ceftazidime in a short infusion of 2g every 8 hours Versus • Ceftazidime in a short infusion of 2g every 8 hours plus teicoplanin of 800mg in two divided doses on the first day and 400mg once a day thereafter Modification by addition or substitution was permitted in cases of marked clinical deterioration, isolation of a resistant pathogen, persistence of presenting bacteremia, diagnosis of a superinfection.

Outcomes:

- Response
- Response after modification
- Treatment failure
- Toxicity
- Bacteriological evaluation

Results:

Death (all cause mortality)
Ceftazidime - 6/50 (12%)
Ceftazidime + teicoplanin - 6/50 (12%)

Death (due to infection)
Ceftazidime - 0/50 (0%)
Ceftazidime + teicoplanin - 0/50 (0%)

Antibiotic resistance
Ceftazidime - 2/51 (4%)
Ceftazidime + teicoplanin - 0/52 (0%)

Proven Bacteraemia
Ceftazidime - 18/51 (35%) (13 caused by gram positive bacteria)
Ceftazidime + teicoplanin - 20/52 (38%) (17 caused by gram positive bacteria)

Toxicity
Nephrotoxicity (defined as 50% increase in creatinine in serum)
Ceftazidime - 3/51 (6%)
Ceftazidime + teicoplanin - 4/52 (8%)

Treatment failure (modifications classed as failure)
Ceftazidime - 26/51 (51%)
Ceftazidime + teicoplanin - 19/52 (37%)

Duration of fever
Ceftazidime
Without modification -3.5 ± 0.8
With modification - 14.6 ± 3.8
Ceftazidime + teicoplanin
Without modification - 3.8 ± 0.9
With modification - 13.6 ± 3.3

Duration of antibiotic therapy
Ceftazidime

Without modification - 7.3 ± 0.8
With modification - 22.4 ± 7.0
Ceftazidime + teicoplanin
Without modification - 7.6 ± 0.8
With modification - 17.4 ± 2.3

Critical care
Not reported

Length of stay
Not reported

Line preservation / "catheter remains in situ"
Not reported

General comments:

- Unclear whether methods of sequence generation and allocation concealment were adequate
- Study was not blinded
- ITT analysis reported for death
- The majority of patients had received oral antimicrobial prophylaxis prior to the onset of fever

8. Ramphal, R., Bolger, M., Oblon, D. J., Sherertz, R. J., Malone, J. D., Rand, K. H. et al. (1992). Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: A randomized prospective study. Antimicrobial Agents and Chemotherapy, 36, 1062-1067
Country: USA
Design: Randomised Controlled Trial
Population: 127 adult febrile neutropenic patients *61% had central lines*
Inclusion criteria: • Underlying neoplastic disease • ≥ 18 years old • Neutropenia (neutrophil count of <500/mm^3 or ≤ 1000/mm^3 and falling • Fever (oral temperature of ≥38°C on two occasions 6h apart or ≥38.5°C on one occasion not associated with blood product transfusions)
Exclusion criteria: • Parenteral antibiotics in the preceding 96 hours • Known allergy to any of the study drugs
Interventions: • Ceftazidime (2g intravenously every 8 hours) Versus • Ceftazidime (2g intravenously every 8 hours) plus vancomycin (1g every 12 hours) Vancomycin was added to the ceftazidime arm when fever persisted for more than 96 hours

Outcomes:

- Death
- Initial response rate
- Duration of fever
- Frequency of new fever
- Microbiological cure
- Superinfection

Results:

Death (all cause)

Ceftazidime + vancomycin - 7/64 (11%)
Ceftazidime - 6/63 (10%)

Death (from infection)

Ceftazidime + vancomycin - 5/64 (8%)
Ceftazidime - 4/63 (6%)

Death (from superinfection)

Ceftazidime + vancomycin - 1/64 (2%)
Ceftazidime - 4/63 (6%)

Super-infection

Ceftazidime + vancomycin - 5/64 (8%)
Ceftazidime – 1/64 (2%)
Ceftazidime (added vancomycin) – 7/? (?%)

Treatment failure (treatment modification considered a failure)

Ceftazidime + vancomycin - 25/64 (39%)
Ceftazidime - 28/63 (44%)

Toxicity
Rashes and renal problems (not reported separately)
Ceftazidime + vancomycin - 19/64 (30%)
Ceftazidime – 6/63 (10%)

Critical care
Not reported

Length of stay
Not reported

Line preservation / “catheter remains in situ”
Not reported

Antibiotic resistance
Not reported

General comments:

- Sequence generation and concealment were adequate
- The study was not blinded
- There were more patients with acute leukaemia and with Hickman catheters in the monotherapy group. These individuals were thought to be higher risk of infection, but the differences did not reach a level of statistical significance.

9. Paul, M., Brook, S., Fraser, A., Vidal, L. & Leibovici, L. (2005) Empirical antibiotics against Gram positive infections for febrile neutropenia: systematic review and meta-analysis of randomised controlled trials. Journal of Antimicrobial Chemotherapy, 55, 436-44

Country:

Israel

Design:

Systematic review

Population:

13 studies including 2392 participants * two studies were concerned with the treatment of persistent fever*

Inclusion criteria:

- Trials comparing a standard antibiotic regimen with a regimen including the addition of an antibiotic with activity against gram-positive bacteria
- Studies assessing empirical intervention both initially and for the treatment of persistent fever

Exclusion criteria:

- Studies with a drop-out rate over 30%

Interventions:

- Standard empirical antibiotic regimen

Versus

- Standard antibiotic regimen with the addition of an antibiotic with activity against gram-positive bacteria

Outcomes:

- All cause mortality

- Treatment failure
- Bacterial superinfection
- Adverse events

Results:

* two studies were concerned with the treatment of persistent fever – the overall results do not therefore apply directly to topic G*

<u>All cause mortality</u>
RR = 0.86 (0.58 – 1.26) P = 0.83; 7 studies; 852 participants

<u>Treatment failure</u>
RR = 1.00 (0.79 – 1.27) P = 0.09; 6 studies; 943 participants

<u>Treatment failure (associated with treatment modifications)</u>
RR = 1.00 (0.61 – 0.80) P = ; 5 studies; 1178 participants

<u>Bacterial superinfection</u>
RR = 0.38 (0.24 – 0.59)

<u>Adverse events</u>
RR = 1.88 (1.10 – 3.22) ; 6 studies; 1282 participants

General comments:

- Only the studies considering initial therapy were relevant to Topic G
- Numerous online databases were searched
- Data was extracted by two reviewers independently
- The quality of studies was assessed by two reviewers using criteria suggested by the Cochrane collaboration
- No significant heterogeneity was present in any of the comparisons
- The authors concluded that the use of glycopeptides could be safely deferred until the documentation of a resistant gram-positive infection