High dose treatment for haematologic malignancies: from rituals to evidence based practice
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Chapter 7

Low bacterial diet versus normal diet to prevent infection in neutropenic cancer patients treated with chemotherapy: Review information

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Abstract

Background: Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infections, which can be life-threatening. It has been hypothesised that a low bacterial diet (LBD) can prevent the occurrence of infections and (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia, but much remains unclear.

Objectives: The primary objective was to determine the efficacy of an LBD versus a control diet in preventing the occurrence of infection and to decrease (infection-related) mortality in adult and paediatric cancer patients receiving chemotherapy causing episodes of neutropenia. Secondary objectives were to assess the time to first febrile episode, the need for empirical antibiotic therapy, diet acceptability and quality of life.

Selection criteria: Randomised controlled trials (RCTs) comparing the use of an LBD with a control diet with regard to infection rate, (infection-related) mortality, time to first febrile episode, need for empirical antibiotic therapy, diet acceptability, and quality of life in adult and paediatric cancer patients receiving chemotherapy causing episodes of neutropenia.

Collection and analysis: Two review authors independently performed the study selection, ‘Risk of bias’ assessment and data extraction. Analyses were performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.

Main results: We identified three RCTs assessing different intervention and control diets in 192 patients (97 randomised to intervention diet; 95 to control diet) with different types of malignancies. Co-interventions (e.g. protective environment, antimicrobial prophylaxis, central venous catheter care, oral care, hygiene practices and colony-stimulating factors) and outcome definitions also differed between studies. In all included studies it was standard policy to give empirical antibiotics (and sometimes also antifungals) to (some of) the patients diagnosed with an infection. Two studies included adults and one study included children. In all studies only a scant description of treatment regimens was provided. All studies had methodological limitations. Pooling of results of included studies was not possible. In two individual studies no statistically significant difference
infection rate between the intervention and control diet was identified; another study showed no significant difference in the number of chemotherapy cycles with an infection between the treatment groups. None of the studies mentioned infection-related mortality, but in one study no significant difference in overall survival between the treatment groups was observed. Time from onset of neutropenia to fever, the duration of empirical antibiotics and antimycotics, diet acceptability (i.e. following the diet easily and following the diet throughout all chemotherapy cycles) and quality of life were all evaluated by only one study; for all outcomes no statistically significant differences between the treatment arms was observed.

Authors’ conclusions: At the moment there is no evidence from individual RCTs in children and adults with different malignancies that underscores the use of an LBD for the prevention of infection and related outcomes. All studies differed with regard to co-interventions, outcome definitions, and intervention and control diets. Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that ‘no evidence of effect’, as identified in this review, is not the same as ‘evidence of no effect’. Based on the currently available evidence, we are not able to give recommendations for clinical practice. More high-quality research is needed.
Neutropenia, defined as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9/L$, is a potentially serious side effect of chemotherapy and high-dose irradiation (MacVittie 1997) and a major risk factor for infection and sepsis. Neutrophils, constituting 55% to 70% of the circulating white blood cells, have the ability to identify, ingest and destroy the majority of foreign invaders (Candell 1991). When the ANC falls to $< 1.0 \times 10^9/L$ there is an increased susceptibility to infection. The frequency and severity of infections is inversely proportional to the neutrophil count and directly proportional to the duration of neutropenia (Hughes 2002). Patients with both solid tumours and hematological malignancies treated with high-dose chemotherapy have a significantly increased risk of developing life-threatening infections. The infection-related mortality in patients with severe neutropenia is approximately 4% to 6% in adult patients and 0.4% to 1.0% in paediatric patients (Hughes 2002; Pizzo 1999; Roguin 1996). At least 50% of the neutropenic patients who become febrile have an established or occult infection and at least 20% of patients with a neutrophil count of $< 0.1 \times 10^9/L$ have bacteraemia (Hughes 2002).

Approximately 80% of the organisms causing infections in neutropenic patients arise from endogenous microbial flora colonising the skin and respiratory, genitourinary and gastrointestinal tracts (Barber 2001). Currently, coagulase-negative staphylococci are the most common blood isolates in most centres; Enterobacteriaceae (i.e. Enterobacter species, *Escherichia coli* and *Klebsiella* species) and non-fermenting gram-negative rods (i.e. *Pseudomonas aeruginosa* and *Stenotrophomonas* species) are isolated less often (Freifeld 2011). Invasive fungal infections are also an important cause of morbidity and mortality. Predisposing factors for fungal infections include the use of broad-spectrum antibiotics, corticosteroids, parenteral nutrition, indwelling intravenous catheters and graft-versus-host disease after an allogeneic stem cell transplantation. The most commonly isolated fungal pathogens are *Aspergillus* and *Candida* species (Barber 2001). Significant advances in supportive care for neutropenic patients have been made since the mid-1990s. Nowadays the supportive care management for neutropenia is directed by risk assessment in adults (Klastersky 2000; Talcott 1992), and evidence-based guidelines for the management of neutropenia and the prevention of opportunistic infections developed by the Centers for Disease Control and Prevention (CDC, US) in both adults and children (Dykewicz 2001; Hughes 2002). These recommendations to prevent
healthcare-associated infections concern the use of antimicrobial prophylaxis, colony-stimulating factors, protective environment, oral care, central venous catheter (CVC) care, hand washing, personal hygiene practices, dietary restrictions and outpatient treatment (Dykewicz 2001). However, despite these achievements, infection continues to be a major cause of morbidity and mortality in the neutropenic patient.

With regards to dietary restrictions it has been hypothesised that a diet for neutropenic patients should reduce pathogens in the gastrointestinal tract by excluding specific foods that may act as a vector for bacteria. The first diet was developed in the 1960s with the intention of providing a completely germ-free diet (Reimer 1966). Since then foods have been sterilised by autoclaving, prolonged baking, gamma irradiation or canning (Aker 1983). Since germ-free diets were considered unpalatable by patients, the US National Institutes of Health, Department of Dietary and Environmental Sanitation, designed the ‘cooked-food’ diet. Although not germ-free, this diet was aimed at eliminating foods with high bacterial counts (Preisler 1970). In a randomised trial, the National Cancer Institute demonstrated that within a decontaminated environment, a germ-free diet gave little advantage over a cooked-food diet with reference to bacterial stool cultures (Preisler 1970). Although the cooked-food diet was more acceptable to patients than the germ-free diet, patients who adhered to this diet for longer than four to six weeks often became frustrated with the food selection (Moody 2002). Occasionally this diet affected their acceptance of other medical therapies as well, which led clinicians to investigate liberalisation of the diet (Pizzo 1982). Pizzo et al cultured 236 commercially available foods and identified < 500 colony-forming units/g in 66% of these foods. They proposed that these foods were acceptable for neutropenic patients. This liberalised diet became known as the low bacterial diet (LBD) (Pizzo 1982).

The role of diet in the risk of infection in patients with neutropenia is still controversial (French 2001). Dietary restrictions vary in the literature and among institutions. Recommendations range from no dietary restrictions to extensive restrictions. Two surveys (French 2001; Smith 2000) indicated that several differences existed in LBDs used by hospitals in the US. Furthermore, there was much variation regarding the initiation and discontinuation point of the LBD. Few clinical studies have been undertaken to assess the efficacy of the LBD in reducing infection rates in neutropenic patients and currently there is no substantial evidence to prove the benefit of the LBD (Larson 2004). As it may pose an unnecessary burden for patients who already have problems with maintaining an adequate oral intake due to complications of high-dose chemotherapy (e.g. mucositis), it would be beneficial to expand
our knowledge regarding the efficacy of LBD. To our knowledge this is the first systematic review in this area.

Objectives

The primary objective was to determine the efficacy of an LBD versus a control diet in preventing the occurrence of infection and to decrease (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia. Secondary objectives were to assess the time to first febrile episode, the need for empirical antibiotic therapy, diet acceptability and quality of life.

Methods

Criteria for considering studies for this review

*Types of studies*
Randomised controlled trials (RCTs) comparing the use of an LBD versus a control diet.

*Types of participants*
Cancer patients who received chemotherapy causing episodes of neutropenia. Both adults and children aged one year and above were eligible for inclusion. Children less than one year of age were excluded due to the large differences in metabolism and feeding patterns.

*Types of interventions*
An LBD versus a control diet. LBD was defined as any diet intended to reduce the ingestion of bacterial and fungal contaminants by the exclusion of foods such as uncooked fruits and vegetables, cold cuts, undercooked eggs and meat, unsterilised water, unpasteurised milk products and soft cheeses. The control diet could be any other diet.

*Types of outcome measures*

*Primary outcomes*
- Infection rate (as defined by the authors of the original studies)
- (Infection-related) mortality (as defined by the authors of the original studies)
Secondary outcomes

- Time to first febrile episode (as defined by the authors of the original studies)
- Need for empirical antibiotic therapy (as defined by the authors of the original studies)
- Diet acceptability (as defined by the authors of the original studies)
- Quality of life (as defined by the authors of the original studies)

Search methods for identification of studies

See: Cochrane Childhood Cancer Group (CCG) and Cochrane Gynaecological Cancer Group (GCG) methods used in reviews (Module CCG 2010; Module GCG 2010).

Electronic searches

The following electronic databases have been searched: the Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, issue 3 2011; including earlier searches in 2008 and 2010), the Database of Abstracts of Reviews of Effects (DARE) (The Cochrane Library, issue 3 2011; including earlier searches in 2008 and 2010), PubMed (from 1946 to 20 October 2011; including earlier searches in 2008 and 2010), EMBASE (from 1980 to 20 October 2011; including earlier searches in 2008 and 2010) and CINAHL (from 1981 to 20 October 2011; including earlier searches in 2008 and 2010). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are stated in the appendices (Appendix 1, Appendix 2, Appendix 3, Appendix 4).

Searching other resources

Information about trials not registered in The Cochrane Library, PubMed, EMBASE or CINAHL, either published or unpublished, was located by searching the reference lists of relevant articles and review articles. The following conference proceedings were searched electronically: American Society of Hematology (ASH; from 2000 to 2011), European Bone Marrow Transplantation (EBMT; from 2000 to 2010), Oncology Nurses Society (ONS; from 2000 to 2011), International Society for Paediatric Oncology (SIOP; from 2000 to 2010), Multinational Association of Supportive Care in Cancer (MASCC; from 2000 to 2010), American Society of Clinical Oncology (ASCO; from 2000 to 2011), Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC; from 2000 to 2011), European Society for Clinical Nutrition and Metabolism (ESPEN; from 2000 to 2011), American Society for Parenteral and Enteral Nutrition (ASPEN; from 2000 to 2011) and European Hematology Association (EHA; from 2000 to 2011) (see Appendix
5 for search terms). We have searched for ongoing trials in the register of
the National Institute of Health and the ISRCTN Register (via controlled-
trials.com; see Appendix 5 for search terms; both were screened in June
2010, October 2011 and May 2012). Researchers working in this area were
contacted to enable identification of ongoing trials. Language restrictions
were not imposed.

Data collection and analysis

Selection of studies
After employing the search strategy described previously, identification
of studies meeting the eligibility criteria were performed by two review
authors independently. We obtained any study in full that seemed to meet
the inclusion criteria on grounds of the title or abstract, or both, for closer
inspection. Reasons for exclusion of any study considered for the review
were clearly stated. Disagreement between the review authors was resolved
by consensus and no third party arbiter was needed.

Data extraction and management
Data extraction was performed independently by two review authors using
standardised forms. Data on study design, characteristics of participants (e.g.
age, sex, disease, treatment, antimicrobial prophylaxis, colony-stimulating
factors, protective environment, oral care, CVC care, hand washing and
hygiene practices), interventions (description of diet in intervention and
control group), outcome measures (as described previously) and length of
follow-up were extracted. Disagreement between the review authors was
resolved by consensus and no third party arbiter was needed.

Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias in included
studies (i.e. selection bias, performance bias, detection bias (for each
outcome separately, with the exception of overall mortality, since for
that outcome blinding was not relevant), attrition bias (for each outcome
separately), reporting bias and other bias). We used the ‘Risk of bias’ items
as described in the module of the CCG (Module CCG 2010), which are based
on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins
2011). Reporting bias was assessed by comparing the methods and results
sections of the manuscript; protocols were not obtained. Disagreement
between the review authors was resolved by consensus and no third party
arbiter was needed. The risk of bias in included studies was taken into
account in the interpretation of the review’s results.
Measures of treatment effect
Dichotomous variables were analysed using risk ratios (RR). All results were presented with the corresponding 95% confidence interval (CI).

Dealing with missing data
When relevant data were missing with regards to study selection, we contacted the principal investigator of the study. Only Van ‘t Veer 1987 was able to provide additional information. We extracted data by the allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. If this was not possible, this was stated and an ‘as treated’ analysis was performed.

Assessment of heterogeneity
Since pooling of results was not possible, the assessment of heterogeneity (both by visual inspection of the forest plot and by a formal statistical test for heterogeneity, i.e. the I² statistic (Higgins 2003; Higgins 2011)) was not applicable.

Assessment of reporting biases
In addition to the evaluation of reporting bias as described in the ‘Assessment of risk of bias in included studies’ section, we planned to assess reporting bias by constructing a funnel plot when there were a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis), because otherwise the power of the tests would be too low to distinguish chance from real asymmetry (Higgins 2011)). But since pooling of results was not possible, this was not applicable.

Data synthesis
We entered data into the Review Manager software as provided by The Cochrane Collaboration (RevMan 2011); analyses were performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). A fixed-effect model was used throughout the review. We performed pooling of results only if study groups were comparable, including the definitions of LBD and the control diet. Studies for which pooling of results was not possible were summarised descriptively.

Sensitivity analysis
Since pooling of results was not possible, sensitivity analyses for ‘Risk of bias’ items (i.e. exclude studies with a high risk of bias and studies for which the risk of bias is unclear and compare the results of studies with a low risk of bias with the results of all available studies) were not applicable.
Results

Description of studies

Results of the search

Running the searches in the electronic databases of CENTRAL, DARE, PubMed, EMBASE and CINAHL yielded a total of 619 references (n = 373 in 2008, n = 75 in 2010 and n = 171 in 2011). Following initial screening of the titles or abstracts, or both, we excluded 612 references that clearly did not meet all criteria for considering studies for this review. The seven remaining references were assessed in full, of which three fulfilled all the criteria for considering studies for this review and were thus eligible for inclusion (Gardner 2008; Moody 2006; Van Tiel 2007). The other four references were excluded for reasons described in the Characteristics of excluded studies table (DeMille 2006; Fopp 1975; Wilson 2002; Ziegler 1992).

Scanning the reference lists of included articles and reviews did not identify any additional eligible studies. By scanning the ongoing trials databases we identified two ongoing trials (see the Characteristics of ongoing studies table). Researchers working in this area were not aware of any ongoing trials. By scanning the conference proceedings we identified one possible eligible study that has not been published in full yet and is thus awaiting further classification (Van ’t Veer 1987; for more information see the Characteristics of studies awaiting classification table), while one study was added to the Characteristics of excluded studies table (Veber 2010).

In summary, the total number of included studies was three. We also identified one study that has not been published in full yet and is awaiting further classification and two ongoing trials. See Figure 1 for a flow diagram of the selection of studies for this systematic review.

Included studies

Characteristics of the included studies are summarised below. For more detailed information see the Characteristics of included studies table. We identified three RCTs (Gardner 2008; Moody 2006; Van Tiel 2007) assessing different intervention and control diets (see Characteristics of included studies table for more detailed information). The total number of patients included in these three RCTs was 192: 97 were randomised to the intervention groups and 95 to the control groups. Two studies included adults (Gardner 2008; Van Tiel 2007), while one study included children (Moody 2006); patients had different types of hematological malignancies or...
solid tumours (in all studies only a scant description of treatment regimens was provided).
Supportive care measures differed between studies. In one study patients were treated in high-efficiency particulate air-filtered rooms (Gardner 2008); in the other studies the use of a protective environment was unclear (Moody 2006; Van Tiel 2007). Patients in two studies received antimicrobial prophylaxis, but the type of agents differed between and within studies (Gardner 2008; Van Tiel 2007); in the other study this was unclear (Moody 2006). Granulocyte colony-stimulating factors were used in part of the patients in two studies (Gardner 2008; Moody 2006); in the other study this was unclear (Van Tiel 2007). In two studies all patients had central lines (Gardner 2008; Moody 2006); in the other study this was unclear (Van Tiel 2007). CVC care was not mentioned in any of the studies. Oral care was not
mentioned in any of the studies. Hygiene practices (including hand washing) were not mentioned in two studies (Gardner 2008; Van Tiel 2007), whereas in the other study all patients received hygiene instructions (Moody 2006).

Risk of bias in included studies

See the ‘Risk of bias’ table of the Characteristics of included studies table and Figure 2 for the exact scores per study and the support for the judgements made.

**Allocation (selection bias)**

For the evaluation of selection bias we have assessed the random sequence generation and the allocation concealment. Both these items, and thus the risk of selection bias, were unclear in one study (Gardner 2008). In the other two studies (Moody 2006; Van Tiel 2007) there was a low risk of selection bias.

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*Figure 2.* ’Risk of bias’ summary: review authors’ judgements about each ’Risk of bias’ item for each included study.
Blinding (performance bias and detection bias)

For the evaluation of performance bias we have assessed the blinding of participants and healthcare providers. In two studies the risk of performance bias was unclear: in Van Tiel 2007 blinding of both participants and healthcare providers was unclear, whereas in Moody 2006 participants were blinded, but for healthcare providers blinding was unclear. In the other study the risk of performance bias was high (Gardner 2008).

For the evaluation of detection bias we have assessed the blinding of outcome assessors for all outcomes separately, with the exception of mortality, since for that outcome blinding was not relevant. Three studies evaluated the infection rate: in two studies the risk of detection bias was unclear (Gardner 2008; Van Tiel 2007), whereas in one study the risk of detection bias was high (Moody 2006). Time to first febrile episode (Moody 2006), need for empirical antibiotic therapy (Van Tiel 2007), diet acceptability (Moody 2006) and quality of life (Moody 2006) were evaluated in only one study; for all these outcomes the risk of detection bias was unclear.

Incomplete outcome data (attrition bias)

For evaluating attrition bias we have assessed incomplete outcome data for all outcomes separately. Three studies evaluated the infection rate: in two studies the risk of attrition bias was low (Gardner 2008; Moody 2006), whereas in the other study this risk was unclear (Van Tiel 2007). The following outcomes were evaluated in only one study: overall survival (Gardner 2008; low risk of attrition bias), time to first febrile episode (Moody 2006; low risk of attrition bias), need for empirical antibiotic therapy (Van Tiel 2007; unclear risk of attrition bias), diet acceptability (Moody 2006; unclear risk of attrition bias) and quality of life (Moody 2006; unclear risk of attrition bias).

Selective reporting (reporting bias)

For evaluating reporting bias we have assessed selective reporting. In all included studies the risk was low.

Other potential sources of bias

For evaluating other potential sources of bias we have assessed differences between the treatment groups for the following items: received anticancer treatment more likely to cause neutropenia, co-interventions (i.e. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices and colony-stimulating factors) and other (as reported in original study).
In two studies the risk of other potential sources of bias was unclear (Gardner 2008; Van Tiel 2007), whereas in the other study the presence of this type of bias could not be ruled out (Moody 2006). For a more detailed description of all different items see the risk of bias section of the Characteristics of included studies table.

**Effects of interventions**

Not all articles allowed data extraction for all end points (see the Characteristics of included studies table for a more detailed description of the extractable end points of each article). All RR, 95% CI and P values mentioned below were calculated in RevMan 2011, unless stated otherwise. Unfortunately, due to differences in co-interventions (i.e. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors), used outcome definitions and intervention and control diets, it was not possible to pool the results of the included studies. Also, Van Tiel 2007 did not present the necessary data to perform adequate analyses (for further information see below).

**Infection rate**

All included studies used different definitions of infection rate. Gardner 2008 assessed the rate of infections (i.e. major infections, minor infections and fever of unknown origin; see Characteristics of included studies table for the exact definition). No statistically significant difference between the treatment groups was identified: 68 out of 78 patients (87%) in the cooked diet group and 57 out of 75 patients (76%) in the raw diet group developed an infection (RR 1.15; 95% CI 0.98 to 1.34; P = 0.08; see Figure 3). Among the 68 infections in the cooked diet group there were 23 major infections (34%), five minor infections (7%) and 40 fevers of unknown origin (59%). In the raw diet group there were 26 major infections (46%), four (7%) minor infections and 27 (47%) fevers of unknown origin. Among the 23 major infections in the cooked diet group there were 12 microbiologically documented infections (52%), whereas among the 26 major infections in the raw diet group there were 22 (85%); this was not reported for minor infections.
infections. Although not explicitly stated, we assumed that in all patients tests to determine the pathogenic organisms were performed. Among the 23 major infections in the cooked diet group there were 12 cases of pneumonia (52%), seven cases of bacteraemia or fungaemia (31%), and four cases of pneumonia and bacteraemia or fungaemia combined (17%), whereas among the 26 major infections in the raw diet group there were four cases of pneumonia (16%), 17 cases of bacteraemia or fungaemia (65%), and five cases of pneumonia and bacteraemia or fungaemia combined (19%); this was not reported for minor infections.

Moody 2006 assessed the rate of neutropenic infections (see Characteristics of included studies table for the exact definition). No statistically significant difference between the treatment groups was identified: four out of nine children (44%) in the US Food and Drug Administration (FDA)-approved food safety guidelines and neutropenic diet guidelines group and four out of 10 children (40%) in the FDA-approved food safety guidelines-only group developed a neutropenic infection (RR 1.11; 95% CI 0.39 to 3.19; P = 0.84; see Figure 4). None of the four neutropenic infections (0%) in the FDA-approved food safety guidelines and neutropenic diet guidelines group were documented (see Characteristics of included studies table for the exact definition), whereas two out of the four neutropenic infections (50%) in the FDA-approved safety guidelines-only group were documented (i.e. one pseudomonas sepsis and one respiratory virus pneumonia).

Van Tiel 2007 did not report the infection rate as number of patients with an infection (defined as a temperature \( \geq 38.5^\circ\text{C} \) or \(< 36^\circ\text{C} \) with a single measurement for which empiric antibiotics were administered), but as number of chemotherapy cycles with infection present. As a result, we could not adequately analyse the infection rate in this study, but we do provide descriptive results: in the LBD group there were 14 chemotherapy cycles with infection present. As a result, we could not adequately analyse the infection rate in this study, but we do provide descriptive results: in the LBD group there were 14 chemotherapy cycles with infection (of which seven were microbiologically confirmed (50%)) among 20 chemotherapy cycles given (70%), whereas in the normal hospital-diet group there were 17 chemotherapy cycles with infection (of which seven were microbiologically confirmed (41%)) among 21 chemotherapy cycles given (81%). No significant difference was observed (P = 0.48 as reported in the original article). Please note that this outcome was assessed in all available chemotherapy cycles, but that it was unclear if all patients were evaluated within these cycles; we can therefore not be certain that an intention-to-treat analysis has been performed.
Infection-related mortality was not mentioned in any of the included studies. Gardner 2008 stated that overall survival (no definition provided) in both treatment groups was as expected in newly diagnosed acute myeloid leukaemia and high-risk myelodysplastic syndrome; no significant difference was observed ($P = 0.36$ as reported in the original article).

**Time to first febrile episode**
Time to fever was evaluated in one study. Moody 2006 identified no significant difference in time to fever (defined as time from onset of neutropenia to fever) between both treatment groups (no further information and no significance level provided).

**Need for empirical antibiotic therapy**
In all included studies it was standard policy to give empirical antibiotics (and sometimes also antymycotics) to (part of) the patients diagnosed with an infection (for more information see the Characteristics of included studies table). Only one study provided explicit data on the use of empirical antibiotics and antymycotics (Van Tiel 2007). In the LBD group the median number of days per chemotherapy cycle with empirical antibiotics and antymycotics was 11 days (range 0 to 22 days) and 0 days (range 0 to 9 days), respectively, whereas in the normal hospital-diet group it was 14.5 days (range 0 to 28 days) and 0 days (0 to 20 days), respectively. No significant difference between treatment groups was detected for duration of empirical antibiotics ($P = 0.09$ as reported in the original article) or duration of empirical antymycotics ($P = 0.96$ as reported in the original article). Please note that it was unclear if this outcome was assessed in all patients; we can therefore not be certain that intention-to-treat analyses have been performed.

**Diet acceptability**
Diet acceptability was evaluated in one study (Moody 2006). In the FDA-approved food safety guidelines and neutropenic diet guidelines group all nine children (100%) reported that they were easily able to follow the guidelines, while seven out of nine children (78%) felt they could follow
them through all chemotherapy cycles. All children (100%) reported some difficulty with the food restrictions, especially avoidance of fast foods and raw fruits. In the FDA-approved guidelines only group nine out of 10 children (90%) reported that they were easily able to follow the guidelines and that they could follow them through all chemotherapy cycles. No significant differences between treatment groups were identified for following the diet easily (RR 1.10; 95% CI 0.84 to 1.45; P = 0.50) and for following the diet throughout all chemotherapy cycles (RR 0.86; 95% CI 0.58 to 1.30; P=0.48) (see Figure 5). Please note that it was not stated if all patients were evaluated for this outcome, although it is likely that they were (it was stated that no patients discontinued the study). An intention-to-treat analysis has been performed.

**Quality of life**

Quality of life was evaluated in one study. Moody 2006 assessed it using the Peds QL Pediatric Quality of Life Inventory Core Module and Cancer Module by self-reports or parent-proxy reports, or both (Varni 2002) and identified no statistically significant changes in score from baseline to follow-up for either arm by child self-report or parent-proxy report (for both the Core and Cancer Modules; no further information provided). Please note that it was not stated if all patients were evaluated for this outcome, although it is likely that they were (it was stated that no patients discontinued the study). However, we are not certain that an intention-to-treat analysis has been performed.

![Figure 5. Forest plot of comparison: 2 FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only, outcome: 2.2 Diet acceptability.](image-url)
Discussion

Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infections, which can be life-threatening. It has been argued that an LBD can prevent the occurrence of infections and (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia, but much remains unclear. To our knowledge this is the first systematic review evaluating this important topic in both adults and children. To ascertain the efficacy of a dietary intervention adequately the best study design, provided that the design and execution are correct, is an RCT in which the only difference between the intervention and control group is the used diet.

We identified three RCTs including a total of 192 patients with different types of hematological malignancies and solid tumours evaluating different intervention and control diets. In all studies only a scant description of treatment regimens was provided. In all included studies it was standard policy to give empirical antibiotics (and sometimes also antifungotics) to (part of) the patients diagnosed with an infection. The first study (Gardner 2008) included adults and defined infection as major infections, minor infections and fever of unknown origin. Patients were randomised to a diet that contained only cooked fruits and vegetables versus a diet that permitted fresh (i.e. raw) fruits and vegetables. Patients were treated in high-efficiency particulate air-filtered rooms and they received antimicrobial prophylaxis. Granulocyte colony-stimulating factors were used in some of the patients. All patients had central lines, but CVC care was not mentioned. Oral care and hygiene practices were not mentioned. The second study (Moody 2006) included children and evaluated neutropenic infections. Patients were randomised between both FDA-approved food safety guidelines and neutropenic diet guidelines versus FDA-approved food safety guidelines only. Granulocyte colony-stimulating factors were used in some of the patients. All patients received hygiene instructions. All patients had central lines, but CVC care was not mentioned. The third study (Van Tiel 2007) included adults and defined infection as a temperature $\geq 38.5\,^\circ\mathrm{C}$ or $< 36\,^\circ\mathrm{C}$ with a single measurement for which empiric antibiotics were administered. Patients were randomised between an LBD and a normal hospital-diet. The use of a protective environment, antimicrobial prophylaxis and oral care was not mentioned.
antimicrobial prophylaxis. It was unclear if patients had central lines; CVC care was not mentioned.

Due to differences in co-interventions (e.g. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices and colony-stimulating factors), used outcome definitions and intervention and control diets, it was not possible to pool the results of the included studies. This should be kept in mind when interpreting the results of the individual studies. Also, one study did not present the necessary data (i.e. the number of patients with an infection) to perform adequate analyses (Van Tiel 2007).

In two individual studies no statistically significant difference in infection rate between patients receiving the intervention and control diet was identified (Gardner 2008; Moody 2006); the study that did not present the necessary data to perform adequate analyses did not show a significant difference in the number of chemotherapy cycles with an infection between the treatment groups (Van Tiel 2007). Infection-related mortality was not mentioned in any of the included studies, but in one study (Gardner 2008) no significant difference in overall survival (no definition provided) between treatment groups was observed. One study (Moody 2006) evaluated time to fever (defined as time from onset of neutropenia to fever) and identified no significant difference between treatment groups. One study provided data on the use of empirical antibiotics and antimycotics apart from infection rate (Van Tiel 2007). Again, no significant difference in duration of empirical antibiotics and antimycotics between the treatment groups was identified. One study evaluated diet acceptability (Moody 2006) and no significant differences between treatment groups were identified for following the diet easily and for following the diet throughout all chemotherapy cycles. Finally, one study evaluated quality of life (Moody 2006) and identified no statistically significant changes in score from baseline to follow-up for either treatment arm by child self-report or parent proxy report.

In this review we tried to perform intention-to-treat analyses, since they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000). However, for the assessment of infection rate and the use of empirical antibiotics by Van Tiel 2007 and quality of life by Moody 2006 it was unclear if these outcomes were assessed in all patients, so we cannot be certain that an intention-to-treat analysis has been performed.

‘No evidence of effect’, as identified in this review, is not the same as ‘evidence of no effect’. The reason that no significant difference between treatment groups was identified could be the fact that the number of patients included in these studies was too small to detect a difference (i.e.
low power). Also, it is possible that baseline imbalances between treatment groups (as included in the other potential sources of bias assessment) played a role.

The risk of bias in the included studies varied. Often bias could not be ruled out due to lack of reporting. However, at the moment this is the best available evidence from RCTs comparing an LBD with a control diet. We are awaiting the results of two ongoing studies (NCT00726934; NCT00947648).

Authors’ conclusions

Implications for practice

At the moment there is no evidence from individual RCTs in children and adults with different malignancies that underscores the use of an LBD for the prevention of infection and related outcomes. All studies differed with regard to co-interventions, used outcome definitions, and used intervention and control diets. Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that ‘no evidence of effect’, as identified in this review, is not the same as ‘evidence of no effect’. Based on the currently available evidence, we are not able to give recommendations for clinical practice.

Implications for research

Before definitive conclusions can be made about the efficacy of different LBDs, more high-quality research is needed. Future trials should preferably be RCTs. They should be performed in homogeneous study populations (e.g. with regards to received anticancer treatment). Also, valid outcome definitions should be used, according to existing guidelines (such as Freifeld 2011). Possible risk factors and preventive measures for neutropenia and infection should be taken into account. The number of included patients should be sufficient to obtain the power needed for the results to be reliable.
Acknowledgements

We thank Nelie Langeveld (Department of Paediatric Oncology, Emma Children’s Hospital/Academic Medical Center, Amsterdam, Netherlands) and Hans van der Lelie (Department of Hematology, Academic Medical Center, Amsterdam, Netherlands) for their help in developing the protocol. We also thank Arnold Leenders (Medical Library of the Academic Medical Center, Amsterdam, Netherlands), for his help with developing the original search strategies for the different databases and for running them and providing us with the titles and abstracts of the searches. Furthermore, we thank A Gardner, K Moody, JMJJ Vossen and FH van Tiel for answering our questions and where possible, providing additional information. Finally, we thank the peer reviewers of this manuscript for their helpful suggestions: Steven Jubelirer, Karen Moody and Mario Cruciani. The editorial base of the Cochrane CCG is funded by Stichting Kinderen Kankervrij (KiKa).

Contributions of authors

Elvira van Dalen performed the data extraction and ‘Risk of bias’ assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the review.

Arno Mank designed the study and wrote the protocol. He identified the studies meeting the inclusion criteria. He contributed to the review manuscript and critically reviewed it.

Edith Leclercq developed the updated search strategy for the CENTRAL, DARE and CINAHL databases and she ran the searches in the different databases for the 2010 and 2011 updates. She identified the studies meeting the inclusion criteria. She contributed to the review manuscript and critically reviewed it.

Renée Mulder performed the data extraction and ‘Risk of bias’ assessment of the included studies. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Michelle Davies designed the study and wrote the protocol. She identified the studies meeting the inclusion criteria. She provided general advice and critically reviewed the review manuscript.

Marie José Kersten provided general advice and critically reviewed the review manuscript.

Marianne van de Wetering designed the study and wrote the protocol. She contributed to the interpretation of the results and provided general advice. She critically reviewed the review manuscript.

All authors approved the final version.
References

References to Included studies


References to Excluded studies


References to Studies awaiting classification

References to Ongoing studies


Additional references


### Characteristics of included studies

**Gardner 2008**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomisation performed by the Leukaemia Department Data Management Office using patients’ early risk of mortality score as a stratification factor</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
<td>153 patients (median age in cooked-diet group 64 years (range 17 to 88 years), median age in raw-diet group 63 years (range 47 to 84 years); sex not reported) with untreated acute myeloid leukaemia (75 in cooked-diet group and 69 in raw-diet group) or high-risk myelodysplastic syndrome (i.e. 10%-19% blasts in marrow or blood) (3 in cooked diet group and 6 in raw diet group). Patients were treated with remission induction chemotherapy on an ongoing leukaemia department protocol</td>
</tr>
</tbody>
</table>
| Interventions | Diet that contained only cooked fruits and vegetables (n = 78) versus diet that permitted fresh (i.e. raw) fruits and vegetables (n = 75)  
Patients in the raw diet group were instructed to eat a fresh fruit or vegetable each day  
All patients were treated in high-efficiency particulate air-filtered rooms  
All patients received antimicrobial prophylaxis with levofloxacin, valacyclovir and, depending on protocol, itraconazole, voriconazole (n = 14 in cooked diet group and n = 8 in raw diet group) or a lipid preparation of amphotericin B; no further information provided  
All patients had central lines; CVC care not reported  
Oral care not reported  
Hygiene practices (including hand washing) not reported  
Granulocyte colony-stimulating factor was used only when there was a delay (i.e. 6 weeks) in neutrophil recovery or after a major infection developed. Its use was equally infrequent in the cooked- and raw-diet groups; no further information provided  
If fever of unknown origin or pneumonia occurred, patients received intravenous ceftazidime or equivalent; if fever did not resolve, antifungal coverage was broadened; no further information provided |
| Outcomes | Infections including:  
- major infections (defined as pneumonia, bacteraemia, fungaemia or pneumonia accompanied by bacteraemia or fungaemia);  
- minor infections (no definition provided);  
- fever of unknown origin (no definition provided)  
A diagnosis of pneumonia required a compatible chest x-ray or computed tomography scan. Bronchoalveolar lavage to isolate a causative organism was performed if no resolution had occurred after 3 to 5 days  
A diagnosis of bacteraemia as a result of frequent contaminants required 2 positive blood cultures  
No definition for a diagnosis of fungaemia was provided  
Overall mortality (no definition provided) |
| Notes | Median number of days on study: 24 days (range 10 to 47 days) in cooked diet group and 24 days (range 6 to 42 days) in the raw diet group. Patients remained on study until they were discharged from the high-efficiency particulate air-filtered room to the outpatient setting, usually after return of the neutrophil count to more than 500/μL or after 6 weeks in patients in whom neutrophil recovery was delayed  
All patients remained on the correct diet while on study, although some did not eat a fresh fruit or vegetable each day as suggested  
There were 206 eligible patients for this study, but 53 refused randomisation; they all choose the cooked fruits and vegetables diet |
<table>
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<tr>
<th>Bias</th>
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</thead>
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<tr>
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<td>Blinding of patients</td>
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<td>Differences between the treatment groups in baseline characteristics related to outcome:</td>
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<td>1) received anticancer treatment more likely to cause neutropenia: unclear (no large difference in types of malignancies, but stage of disease and exact treatment including doses not reported)</td>
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<td>2) co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences for protective environment, antimicrobial prophylaxis and colony-stimulating factor use; not reported for the other items (maybe not used at all)</td>
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<td>3) other (as reported in original study): not reported</td>
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### Methods
Random numbering was used to assign patients to the treatment groups; patients were randomised in blocks of 10, stratified by disease (i.e. leukaemia, brain tumour or sarcoma).

### Participants
19 children (aged 18 years or less, median age in the neutropenic diet group 4.4 years, median age in the FDA food safety group 4.1 years; 8 boys and 11 girls) with a medulloblastoma (2 in each group), acute lymphocytic leukaemia (5 in each group), osteosarcoma (2 in each group) or Ewing’s sarcoma (1 patient in the FDA food safety group). Patients were on active treatment with myelosuppressive chemotherapy. Exclusion criteria included comorbid immunosuppressive disease, myeloablative chemotherapy in preparation for bone marrow transplant, documented fever or infection at time of enrolment, patients who could not tolerate oral feeding and concurrent radiation to the central nervous system or gastrointestinal tract.

### Interventions
Both FDA-approved food safety guidelines (Food Safety 2005) and neutropenic diet guidelines (i.e. not eating raw fruits (except for fruits that could be peeled by hand, such as oranges and bananas), raw vegetables, aged cheeses, cold meat cuts, fast food and take-out food; cook all produce to well done, eggs must be hard-boiled) (n = 9) versus FDA-approved food safety guidelines only (n = 10). Patients were instructed to start following their diet on the first day of the chemotherapy cycle and to continue it until completion of the study period.

### Outcomes
Infections including:
- neutropenic infections operationalised to include febrile neutropenia defined as either an oral temperature of ≥ 38°C as measured by parent or documented by clinic/hospital staff and an ANC < 500 x 10⁹/L or admission to hospital and treatment with broad-spectrum antibiotics for presumed infection and an ANC < 500 x 10⁹/L;
- documented infections such as positive blood, urine, stool or sputum cultures or positive radiographic evidence of infection including abscess, pneumonia or typhlitis

### Notes
Length of follow-up: not reported (median number of chemotherapy cycles in the neutropenic diet group 5 and in the FDA food safety group 4; no significant difference). Patients were followed until neutrophil recovery (defined as an ANC > 500 x 10⁹/L on 2 consecutive complete blood counts).

All patients received their assigned diet and the planned chemotherapy. Diet adherence rate was 94.1% in the intervention group and 99.99% in the control group. There were 21 eligible patients for this study, but 2 were not included: 1 refused to participate because of depression and 1 suffered from a new-onset psychosis and was therefore not approached.

At baseline there were statistically significant differences between treatment groups in history of febrile neutropenia (all patients in the neutropenic diet group versus 5 out of 10 patients in the FDA food safety group) and in quality of life (core module lower in the neutropenic diet group; no significant differences in the cancer module; the authors state that this is most likely secondary to the small sample size).
## Risk of bias table

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<td>It was stated that the patients’ diet allocation was concealed from the investigator until after the patient consented to participate in the study</td>
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<td>It was stated that patients and their parents were blinded to the intervention</td>
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</table>
Methods Randomisation performed by using a pre-determined randomisation schedule produced by a computerised randomisation program

Participants 20 cytopenic patients (mean age in the LBD group 51.8 years (range 40 to 69 years), mean age in the normal hospital-diet group 53.3 years (range 30 to 68 years); 5 women and 15 men) with acute lymphoblastic leukaemia (4 in the LBD group and 1 in the normal hospital-diet group: see notes) or acute myelogenous leukaemia (6 in the LBD group and 9 in the normal hospital-diet group: see notes). Patients were treated with remission induction chemotherapy; no further information provided (see notes)

Interventions LBD (i.e. omits raw vegetables, salads, soft cheeses, raw meat products, most fresh fruits, tap water and spices added after cooking; bread, cheese and ham are individually packed and yogurt deserts, soda drinks and soups are served in single serving containers) (n = 10) versus normal hospital-diet (no further information provided) (n = 10)

Patients started their assigned treatment as soon as possible after inclusion

Protective environment: not reported

All patients received antimicrobial prophylaxis including ciprofloxacin (500 mg every 12 hours, orally) and fluconazole (50 mg every 24 hours, orally). It was adjusted or switched to alternative drugs according to the results of the surveillance cultures; no further information provided. It was started before initiation of chemotherapy and discontinued when leukocyte counts had recovered to ≥ 1000/mm³

It was unclear if patients had central lines; CVC care: not reported

Oral care, hygiene practices (including hand washing) and use of colony-stimulating factors: not reported

Outcomes Infection (defined as a temperature ≥ 38.5°C or < 36°C with a single measurement for which empiric antibiotics were administered)

Duration of empirical antibiotics or antimycotics (no definition provided)

Notes Length of follow-up: not reported (total number of chemotherapy cycles in the LBD group was 20 and in the normal hospital-diet group 20; total number of days within chemotherapy cycles was 406 in the LBD group and 509 in the normal hospital-diet group, it was not stated if this was a significant difference; median number of days per chemotherapy cycle in the LBD group was 18 (range 4 to 34 days per chemotherapy cycle) and in the normal hospital-diet group 24 (range 1 to 39 days per chemotherapy cycle), this was not a significant difference)

All patients received their assigned diet

Number of eligible patients that were not randomised: not reported

It was not stated if the difference in diagnoses (i.e. acute lymphoblastic leukaemia or acute myelogenous leukaemia) between the treatment groups were significant. Also, the exact treatment patients with each diagnosis received was not reported, thus making it impossible to know if patients in 1 of the treatment groups received treatment more likely to cause neutropenia
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Footnotes ANC: absolute neutrophil count; CVC: central venous catheter; FDA: Food and Drug Administration; LBD: low bacterial diet; n: number.

Characteristics of excluded studies

**DeMille 2006**
Reason for exclusion: No RCT; no control group

**Fopp 1975**
Reason for exclusion: No randomisation of LBD versus a control diet

**Veber 2010**
Reason for exclusion: No RCT; infection not evaluated

**Wilson 2002**
Reason for exclusion: No RCT; review

**Ziegler 1992**
Reason for exclusion: No evaluation of an LBD versus control treatment

Footnotes LBD: low bacterial diet; RCT: randomised controlled trial.

Characteristics of studies awaiting classification

**Van ’t Veer 1987**
Methods: RCT, but method of randomisation not clear
Participants: 42 granulocytopenic children (age (see notes) and sex not reported) with aplastic anaemia, acute lymphocytic leukaemia, acute non-lymphocytic leukaemia or granulocytopenia of unknown origin. Anticancer treatment not reported
Interventions: Cooked-food diet versus standard hospital-food (numbers per group not reported). All patients received partial protective isolation and selective gastrointestinal decontamination
Van ’t Veer 1987 (Continued)

Outcomes 42 children had 55 episodes (29 episodes in cooked-food group and 26 episodes in standard hospital-food group) of at least 10 days with granulocyte counts below 500/μL

Cooked-food diet (637 study days):
- 3 septicaemias, 2 major infections, 2 minor infections and 5 episodes of fever of unknown origin; no deaths from infections;
- number of infections per 1000 days at risk (i.e. granulocytes < 500/μL): 11.0 days;
- number of febrile episodes per 1000 days at risk (i.e. granulocytes below 500/μL): 7.8 days

Standard hospital-food diet (925 study days):
- 9 septicaemias, 5 minor infections and 13 episodes of fever of unknown origin; no deaths from infections;
- number of infections per 1000 days at risk (i.e. granulocytes below 500/μL): 15.1 days;
- number of febrile episodes per 1000 days at risk (i.e. granulocytes below 500/μL): 14.1 days;
- number of infections per 1000 days at risk and number of febrile episodes per 1000 days at risk: no significant differences between the treatment groups;
- for all other outcomes no level of significance for the difference was mentioned

No definitions of the mentioned outcomes were provided

Notes This study has not been published in full text (checked December 2011); the information provided here is based on a conference abstract of the 1997 edition of the Annual Meeting of the American Society of Hematology and additional information provided by the authors (i.e. from the abstract it was not clear that the participants were children, however, the authors were only able to confirm that participants were indeed children, the exact age range was not provided by them). From the currently available data it is unclear if this study fulfils all inclusion criteria for this review

Footnotes RCT: randomised controlled trial.

Characteristics of ongoing studies

NCT00726934

Study name The effectiveness of the neutropenic diet in paediatric oncology patients

Methods Method of randomisation not clear

Participants Patients (aged 1 to 30 years) with different paediatric malignancies receiving a cycle of chemotherapy that predictably renders neutropenia at least 70% of the time or has a risk of febrile neutropenia of at least 20%

Interventions Low bacterial/neutropenic diet (e.g. excluding raw food and vegetables) versus FDA-approved food safety guidelines

Outcomes Neutropenic infection, documented infection and quality of life

Starting date sep-07

Contact information Principal investigator Karen Moody

Notes No full-text publication available as per 17 May 2012
<table>
<thead>
<tr>
<th><strong>NCT00947648</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study name</strong></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
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<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
</tbody>
</table>

*Footnotes* FDA: Food and Drug Administration.
## Data and analyses

### Comparison 1. Cooked diet versus raw diet

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Infections (i.e. major infection, minor infection and fever of unknown origin)</td>
<td>1</td>
<td>153</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.15 [0.98, 1.34]</td>
</tr>
</tbody>
</table>

### Comparison 2. FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Neutropenic infection</td>
<td>1</td>
<td>19</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.11 [0.39, 3.19]</td>
</tr>
<tr>
<td>2.2 Diet acceptability</td>
<td>1</td>
<td></td>
<td></td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.2.1 Diet was easy to follow</td>
<td>1</td>
<td>19</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.10 [0.84, 1.45]</td>
</tr>
<tr>
<td>2.2.2 Able to follow diet throughout all chemotherapy cycles</td>
<td>1</td>
<td>19</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.86 [0.58, 1.30]</td>
</tr>
</tbody>
</table>

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**Analysis 1.1.** Comparison 1 Cooked diet versus raw diet, Outcome 1 Infections (i.e. major infection, minor infection and fever of unknown origin)
Appendices

1 PubMed search strategy

bone marrow transplantation[mesh] OR bone marrow transplantation[tw]
OR cytopen*[tw] OR stem cell transplantation[mesh] OR stem cell transplantation[tw] OR agranulocytosis[mesh] OR agranulocytosis[tw]
OR bacterial translocation[mesh] OR bacterial translocation[tw] OR immunocompromised host[mesh] OR immunocompromised host[tw]
OR neutropeni*[tiab] OR leukopeni*[tiab] OR leucopeni*[tiab]
[tw = text word; tiab = title or abstract; mesh = medical subject heading; * = zero or more characters]

2 EMBASE (Ovid) search strategy
1 agranulocytosis.mp. or exp AGRANULOCYTOSIS/
2 stem cell transplantation.mp. or exp stem cell transplantation/
3 bone marrow transplantation.mp. or exp bone marrow transplantation/
4 bacterial translocation.mp. or exp Bacterial Translocation/
5 exp Immune Deficiency/
6 (neutropeni$ or leukopeni$ or cytopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised).tw.
7 or/1-6
8 (sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$).tw.
9 exp Diet/
10 (diet$ or water or feeding or food$ or nutrition).tw.
11 8 and (9 or 10)
12 dietary restriction$.tw.
13 11 or 12
14 7 and 13
[tw = text word; / = Emtree term; $ = zero or more characters; mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

3 CENTRAL and DARE (The Cochrane Library) search strategy
1 MeSH descriptor Agranulocytosis explode all trees in MeSH products
2 MeSH descriptor Bacterial Translocation explode all trees in MeSH products
3 MeSH descriptor Immunocompromised Host explode all trees in MeSH products
4 (agranulocytosis or bacterial translocation or immunocompromised or cytopeni* or immunocompromized or neutropeni* or leukopeni* or leucopeni* or granulocytopeni*)
5 (1 OR 2 OR 3 OR 4)
6 MeSH descriptor Diet explode all trees in MeSH products
7 (low near bacteria* or low near microbia* or minimal near bacteria* or minimal near microbia* or germ near poor or neutropenic or cooked or reduced near bacteria* or sterile or clean)
8 (diet* or feeding or food* or water or nutrition)
9 (6 OR 8)
10 (dietary restriction*)
11 ((7 AND 9) OR 10)
12 (5 AND 11)
13 (dietary near restriction*)
16 (12)
17 MeSH descriptor Bone Marrow Transplantation explode all trees
18 MeSH descriptor Stem Cell Transplantation explode all trees
19 (bone marrow transplantation ):ti,ab,kw or (stem cell transplantation):ti,ab,kw
20 (5 OR 17 OR 18 OR 19)
21 (7 AND 8)
22 (21 OR 13)
23 (20 AND 22)

Adjusted search strategy used in June 2010 and October 2011:
1 MeSH descriptor Agranulocytosis explode all trees
2 MeSH descriptor Bacterial Translocation explode all trees
3 MeSH descriptor Immunocompromised Host explode all trees
4 (agranulocytosis or bacterial translocation or immunocompromised or cytopeni* or immunocompromized or neutropeni* or leukopeni* or leucopeni* or granulocytopeni*)
5 (1 OR 2 OR 3 OR 4)
6 MeSH descriptor Diet explode all trees
7 (low near bacteria* or low near microbia* or minimal near bacteria* or minimal near microbia* or germ near poor or neutropenic or cooked or reduced near bacteria* or sterile or clean)
8 (diet* or feeding or food* or water or nutrition)
9 (dietary restriction*)
10 (dietary near restriction*)
11 (6 OR 7 OR 8 OR 9 OR 10)
12 MeSH descriptor Bone Marrow Transplantation explode all trees
13 MeSH descriptor Stem Cell Transplantation explode all trees
14 (bone marrow transplantation) or (stem cell transplantation):ti,ab,kw
15 (5 OR 12 OR 13 OR 14)
16 (11 AND 15)

[ti,ab,kw = title or abstract or keywords; * = zero or more characters]

4 CINAHL search strategy

S1 AB sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or ger poor or neutropenic or cooked or reduced bacteria$
S2 TI sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or ger poor or neutropenic or cooked or reduced bacteria$
S3 S2 or S1
S4 MH diet+
S5 AB diet$ or water or feeding or food$ or nutrition
S6 TI diet$ or water or feeding or food$ or nutrition
S7 S6 or S5
S8 S7 or S4
S9 S8 and S3
S10 MH agranulocytosis+ or bacterial translocation+ or bone marrow transplantation+ or immunocompromised host+
S11 AB neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromised or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S12 TI neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromised or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S13 S12 or S11 or S10
S14 AB dietary restriction$
S15 TI dietary restriction$
S16 S15 or S9
S17 (S15 or S9) and (S16 and S13)

Adjusted search strategy used in June 2010 and October 2011:

S1 AB sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or ger poor or neutropenic or cooked or reduced bacteria$
5 Ongoing trial registers and conference proceedings search strategies

We have searched the register of the National Institutes of Health and the ISRCTN register (via www.controlled-trials.com) with the following key words: low bacterial AND diet; neutropenic AND diet; low bacterial AND cancer.

The conference proceedings (ASH, ASCO, ASPEN, EBMT, EHA, ESPEN, ICAAC, MASCC, ONS and SIOP) were searched electronically using the following search terms: “neutropenic diet”, “low bacterial”, “hospital diet”, “normal diet”, and LBD.