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Low bacterial diet versus control diet to prevent infection in cancer patients treated with chemotherapy causing episodes of neutropenia (Review)

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[Intervention Review]

Low bacterial diet versus control diet to prevent infection in cancer patients treated with chemotherapy causing episodes of neutropenia

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ABSTRACT

Background

Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infection, which can be life-threatening. It has been hypothesised that a low bacterial diet (LBD) can prevent infection and (infection-related) mortality in cancer patients receiving chemotherapy that causes episodes of neutropenia, but much remains unclear. This review is an update of a previously published Cochrane review.

Objectives

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

Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 4), the Database of Abstracts of Reviews of Effects (DARE) (2015, Issue 4), PubMed (from 1946 to 4 May 2015), EMBASE (from 1980 to 4 May 2015) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from 1981 to 4 May 2015).

In addition, we searched the reference lists of relevant articles and conference proceedings of American Society of Hematology (ASH; from 2000 to 2015), European Bone Marrow Transplantation (EBMT; from 2000 to 2015), Oncology Nurses Society (ONS; from 2000 to 2015), International Society for Paediatric Oncology (SIOP; from 2000 to 2014), Multinational Association of Supportive Care in Cancer (MASCC; from 2000 to 2015), American Society of Clinical Oncology (ASCO; from 2000 to 2015), Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC; from 2000 to 2015), European Society for Clinical Nutrition and Metabolism (ESPEN; from 2000 to 2015), American Society for Parenteral and Enteral Nutrition (ASPEN; from 2000 to 2015) and European Hematology Association (EHA; from 2000 to 2015). In May 2015, we scanned the National Institutes of Health Register via clinicaltrials.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) Register (www.controlled-trials.com).

Selection criteria

Randomised controlled trials (RCTs) comparing use of an LBD versus 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.

Data collection and analysis

Two review authors independently performed study selection, 'Risk of bias' assessment and data extraction. We performed analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

In the original version of this review, we identified three RCTs that assessed different intervention and control diets in 192 participants (97 randomised to intervention diet; 95 to control diet) with different types of malignancies. For the update, we identified no eligible new studies. Co-interventions (e.g. protective environment, antimicrobial prophylaxis, central venous catheter care, oral care, hygiene practices, 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 antimycotics) to (some of) the participants 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 differences in infection rate were identified between intervention and control diets; another study showed no significant differences between treatment groups in the number of chemotherapy cycles with an infection. None of the studies mentioned infection-related mortality, but in one study, no significant difference in overall survival was observed between treatment groups. Time from onset of neutropenia to fever, 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 treatment arms were identified.

Authors' conclusions

At the moment, no evidence from individual RCTs in children and adults with different malignancies underscores use of an LBD for prevention of infection and related outcomes. All studies differed with regard to co-interventions, outcome definitions and intervention and control diets. As pooling of results was not possible, and as all studies had serious methodological limitations, we could reach no definitive conclusions. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. On the basis of currently available evidence, we are not able to provide recommendations for clinical practice. Additional high-quality research is needed.

PLAIN LANGUAGE SUMMARY

Low bacterial diet versus control diet to prevent infection in cancer patients treated with chemotherapy causing episodes of neutropenia

Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infection, which can be life-threatening. It has been argued that a low bacterial diet (i.e. food and drinks with low levels of bacteria) can prevent the occurrence of infection and (infection-related) death in cancer patients receiving chemotherapy that causes episodes of neutropenia.

Review authors identified three randomised studies comparing different diets in 192 children and adults with different types of cancer. Other interventions, such as antimicrobial prophylaxis (i.e. prevention of infection via antimicrobial therapy such as antibiotics) and hygiene practices, and definitions of study outcomes also differed between studies, and very limited information on anticancer treatment was given. All studies had methodological problems. Unfortunately, combining the results of included studies was not possible, but at the moment, no evidence from individual studies suggests that a low bacterial diet prevents infection. Data on survival, time from onset of neutropenia to start of fever, duration of empirical (i.e. start of treatment before determination of a definitive diagnosis) antibiotics and antimycotics (i.e. agents that target fungal infection), diet acceptability and quality of life all were evaluated by only one study; for all outcomes, no statistically significant differences between treatment groups were observed. None of the studies evaluated infection-related mortality. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. No differences between diets were identified, possibly because few patients were included in these studies. On the basis of currently available evidence, the review authors were not able to give recommendations for clinical practice. Additional high-quality research is needed.

BACKGROUND

Neutropenia, defined as an absolute neutrophil count (ANC) $< 0.5 \times 10^9/L$, 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 circulating white blood cells, have the ability to identify, ingest and destroy most foreign invaders (Candell 1991). When the ANC falls to $< 1.0 \times 10^9/L$, susceptibility to infection is increased. The frequency and severity of infections are inversely proportional to the neutrophil count and are directly proportional to the duration of neutropenia (Hughes 2002). Patients with both solid tumours and haematological malignancies treated with high-dose chemotherapy have a significantly increased risk of developing life-threatening infection.

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 neutropenic patients who become febrile have an established or occult infection, and at least 20% with a neutrophil count $< 0.1 \times 10^9/L$ have bacteraemia (Hughes 2002).

Approximately 80% of the organisms that cause infection 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; 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 infection is another important cause of morbidity and mortality. Predisposing factors for fungal infection include use of broad-spectrum antibiotics, corticosteroids, parenteral nutrition and indwelling intravenous catheters, along with 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, supportive care management for neutropenia is directed by risk assessment in adults (Klastersky 2000; Talcott 1992) and by evidence-based guidelines for management of neutropenia and prevention of opportunistic infection developed by the Centers for Disease Control and Prevention (CDC, USA) for both adults and children (Dykewicz 2001; Hughes 2002). These recommendations to prevent healthcare-associated infection involve antimicrobial prophylaxis, colony-stimulating factors, a 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 among neutropenic patients.

With regard 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 such diet was developed in the 1960s with the intention of providing a completely germ-free diet (Reimer 1966). Since that time, foods have been sterilised by

autoclaving, prolonged baking, gamma irradiation or canning (Aker 1983). Germ-free diets were considered unpalatable; therefore, 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 offered 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 fewer than 500 colony-forming units per gram in 66% of these foods. Investigators 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 among patients with neutropenia remains 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) revealed several differences among LBDs used by hospitals in the USA. Furthermore, much variation was reported regarding initiation and discontinuation of the LBD. Few clinical studies have been undertaken to assess the efficacy of the LBD in reducing infection among neutropenic patients, and currently no substantial evidence is available to prove the benefit of the LBD (Larson 2004). As the LBD may pose an unnecessary burden for patients who already have problems with maintaining adequate oral intake because of complications of high-dose chemotherapy (e.g. mucositis), it would be beneficial to expand our knowledge regarding the efficacy of this diet. This review serves as an update of the first systematic review (Mank 2012) conducted to evaluate the state of evidence on low bacterial diet versus control diet for preventing infection in cancer patients treated with chemotherapy that causes episodes of neutropenia.

OBJECTIVES

The primary objective of this review was to determine the efficacy of an LBD versus a control diet in preventing infection and in decreasing (infection-related) mortality in adult and paediatric cancer patients receiving chemotherapy that causes episodes of neutropenia. Secondary objectives were to assess time to first febrile episode, 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 use of an LBD versus a control diet.

Types of participants

Cancer patients who received chemotherapy causing episodes of neutropenia. Both adults and children one year of age and older were eligible for inclusion. Children younger than one year of age were excluded because of 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 ingestion of bacterial and fungal contaminants through 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 authors of the original studies).
- (Infection-related) mortality (as defined by authors of the original studies).

Secondary outcomes

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

In the original version of the review, review authors searched the following electronic databases: the Central Register of Controlled Trials (CENTRAL) (2011, Issue 3; including earlier searches in 2008 and 2010), the Database of Abstracts of Reviews of Effects (DARE) (2011, Issue 3; 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 the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from 1981 to 20 October 2011; including earlier searches in 2008 and 2010). Search strategies used 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](#)).

For the update, we repeated the same searches in CENTRAL and DARE (2015, Issue 4), PubMed (2011 to 4 May 2015), EMBASE (from 2011 to 4 May 2015) and CINAHL (from 2011 to 4 May 2015).

Searching other resources

In the original version of the review, we found information about trials not registered in *The Cochrane Library*, PubMed, EMBASE or CINAHL, published or unpublished, by searching the

reference lists of relevant articles and review articles. We searched the following conference proceedings 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 searched for ongoing trials in the register of the National Institutes of Health (via [clinicaltrials.gov](#)) and the International Standard Randomised Controlled Trial Number (ISRCTN) Register (via [controlled-trials.com](#); see [Appendix 5](#) for search terms; we screened both in June 2010, October 2011 and May 2012). We contacted researchers working in this area to identify ongoing trials. We imposed no language restrictions.

For the update, we searched the above mentioned conference proceedings from 2011 or 2012 until 2015, except for SIOP abstracts (until 2014), and we searched ongoing trial registries in May 2015, all by using the same keywords as mentioned in the appendices. In addition, we searched the reference lists of relevant articles and review articles.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, two review authors independently identified studies meeting the eligibility criteria of this review. We obtained in full text for closer inspection any study that seemed to meet the inclusion criteria upon review of the title, the abstract or both. We clearly stated reasons for exclusion of any study considered for the review. We resolved disagreements between review authors by consensus, with no need for a third party arbiter.

Data extraction and management

Two review authors independently extracted data by using standardised forms. We extracted 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, hygiene practices), interventions (description of diet in intervention and control group), outcome measures (as described previously) and length of follow-up. We resolved disagreements between review authors by consensus, with no need for a third party arbiter.

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, because for that outcome, blinding was not relevant), attrition bias (for each outcome separately), reporting bias and other bias). We used '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). We assessed reporting bias by comparing the methods and results sections of the manuscript; we did not obtain protocols. We resolved disagreements between review authors by consensus, with no need for a third party arbiter. We considered the risk of bias in included studies when interpreting results of the review.

Measures of treatment effect

We analysed dichotomous variables by using risk ratios (RRs). We presented all results with corresponding 95% confidence intervals (CIs).

Dealing with missing data

When relevant data were missing with regards to study selection, we contacted the principal investigator of the study. Only researchers of [Van 't Veer 1987](#) were able to provide additional information. We extracted data by the allocated intervention, irrespective of compliance with treatment, to allow an intention-to-treat analysis. If this was not possible, we stated this and performed an 'as treated' analysis.

Assessment of heterogeneity

Pooling of results for this review was not possible; therefore, assessment of heterogeneity (both by visual inspection of the forest plot and by formal statistical testing for heterogeneity, i.e. the I^2 statistic ([Higgins 2003](#); [Higgins 2011](#))) was not applicable.

Assessment of reporting biases

In addition to evaluating 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 we had identified 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 allow us to distinguish chance from real asymmetry ([Higgins 2011](#)). As pooling of results was not possible, this was not applicable.

Data synthesis

We entered data into Review Manager software as provided by The Cochrane Collaboration ([RevMan 2014](#)); we performed analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We used a fixed-effect model throughout the review and pooled results only when study groups were comparable, including definitions of LBD and control diet. We summarised descriptively studies for which pooling of results was not possible.

Sensitivity analysis

As pooling of results was not possible, sensitivity analyses for 'Risk of bias' items (i.e. excluding studies with high risk of bias and

studies for which risk of bias was unclear and comparing results of studies with low risk of bias vs results of all available studies) were not applicable.

RESULTS

Description of studies

Results of the search

Searches conducted for the original version of this review using 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). After initial screening of titles or abstracts, or both, we excluded 612 references that clearly did not meet all criteria for inclusion of studies in this review. We assessed the seven remaining references in full; three fulfilled all criteria and thus were deemed eligible for inclusion ([Gardner 2008](#); [Moody 2006](#); [Van Tiel 2007](#)). We excluded the other four references for the reasons described in the [Characteristics of excluded studies](#) table ([DeMille 2006](#); [Fopp 1975](#); [Wilson 2002](#); [Ziegler 1992](#)).

A scan of the reference lists of included articles and reviews revealed no 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 conference proceedings, we identified one possibly eligible study that has not been published in full yet and thus is awaiting further classification ([Van 't Veer 1987](#); for more information, see the [Characteristics of studies awaiting classification](#) table), and we added one study to the [Characteristics of excluded studies](#) table ([Veber 2010](#)).

Searches of CENTRAL and DARE, PubMed, EMBASE/Ovid and CINAHL/EBSCO for this update yielded a total of 558 references; 495 records remained after deduplication. After screening titles and abstracts, we excluded 489 studies, and we assessed six studies as full text. We excluded all six studies for reasons described in the [Characteristics of excluded studies](#) table ([Carr 2014](#); [Foster 2014](#); [Brown 2014](#); [Lund 2014](#); [Fox 2012](#); [Trifilio 2012](#)). We identified no studies by searching conference proceedings, ongoing trial registries and reference lists of the six assessed studies and reviews identified in the update.

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 studies selected for this update.

Figure 1. Flow diagram of study selection.

Included studies

We have summarised characteristics of the included studies below. For more detailed information, see the [Characteristics of included studies](#) table.

We identified three RCTs ([Gardner 2008](#); [Moody 2006](#); [Van Tiel 2007](#)) conducted to assess different intervention and control diets (see [Characteristics of included studies](#) table for more detailed information). The total number of participants included in these three RCTs was 192: 97 were randomised to intervention groups and 95 to control groups. Two studies included adults ([Gardner 2008](#); [Van Tiel 2007](#)), and one study included children ([Moody 2006](#)); participants had different types of haematological malignancies or solid tumours (all studies provided only a scant description of treatment regimens).

Supportive care measures differed between studies. Investigators in one study treated participants in high-efficiency particulate air-filtered rooms ([Gardner 2008](#)); in the other studies, use of a

protective environment was unclear ([Moody 2006](#); [Van Tiel 2007](#)). Investigators in two studies provided antimicrobial prophylaxis for participants, but types of agents differed between and within studies ([Gardner 2008](#); [Van Tiel 2007](#)); in the other study, this treatment was unclear ([Moody 2006](#)). Two studies used granulocyte colony-stimulating factors for some participants ([Gardner 2008](#); [Moody 2006](#)); in the other study, this treatment was unclear ([Van Tiel 2007](#)). Two studies used central lines for all participants ([Gardner 2008](#); [Moody 2006](#)); in the other study, this treatment was unclear ([Van Tiel 2007](#)). No studies mentioned CVC care, and no studies mentioned oral care. Two studies did not mention hygiene practices (including hand washing) ([Gardner 2008](#); [Van Tiel 2007](#)), whereas investigators in the other study provided hygiene instructions for all participants ([Moody 2006](#)).

Risk of bias in included studies

See the 'Risk of bias' table under [Characteristics of included studies](#) and [Figure 2](#) for exact scores per study and support for judgements made.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients (performance bias)	Blinding of health care providers (performance bias)	Blinding of outcome assessors (detection bias): infections	Blinding of outcome assessors (detection bias): time to first febrile episode	Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	Blinding of outcome assessor (detection bias): diet acceptability	Blinding of outcome assessor (detection bias): quality of life	Incomplete outcome data (attrition bias): infections	Incomplete outcome data (attrition bias): overall survival	Incomplete outcome data (attrition bias): time to first febrile episode	Incomplete outcome data (attrition bias): duration of empirical antibiotics and antimycotics	Incomplete outcome data (attrition bias): diet acceptability	Incomplete outcome data (attrition bias): quality of life	Selective reporting (reporting bias)	Other bias
Gardner 2008	?	?	-	-	?					+	+					+	?
Moody 2006	+	+	+	?	-	?		?	?	+		+		?	?	+	-
Van Tiel 2007	+	+	?	?	?		?			?			?			+	?

Allocation

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

Blinding

For evaluation of performance bias, we assessed blinding of participants and healthcare providers. In two studies, risk of

performance bias was unclear: In [Van Tiel 2007](#), blinding of both participants and healthcare providers was unclear, and in [Moody 2006](#), participants were blinded, but blinding of healthcare providers was unclear. In the other study, risk of performance bias was high ([Gardner 2008](#)).

For evaluation of detection bias, we assessed blinding of outcome assessors for all outcomes separately, with the exception of mortality, because for that outcome, blinding was not relevant. Three studies evaluated the infection rate: In two studies, risk of detection bias was unclear ([Gardner 2008](#); [Van Tiel 2007](#)), and in one

study, 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 of these outcomes, risk of detection bias was unclear.

Incomplete outcome data

For evaluation of attrition bias, we assessed incomplete outcome data for all outcomes separately. Three studies evaluated the infection rate: In two studies, risk of attrition bias was low (Gardner 2008; Moody 2006), and 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

For evaluation of reporting bias, we assessed selective reporting. In all included studies, the risk was low.

Other potential sources of bias

For evaluation of other potential sources of bias, we assessed differences between 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 the original study).

In two studies, the risk of other potential sources of bias was unclear (Gardner 2008; Van Tiel 2007), and in the other study, we could not rule out the presence of this type of bias (Moody 2006). For a more detailed description of all items, see the 'Risk of bias' section of the [Characteristics of included studies](#) table.

Effects of interventions

None of the articles did allow data extraction for all end points (see the [Characteristics of included studies](#) table for a more

detailed description of extractable end points for each article). We calculated all RRs, 95% CIs and P values mentioned below in [RevMan 2014](#), unless stated otherwise.

Unfortunately, because of differences in co-interventions (i.e. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors), outcome definitions used and intervention and control diets provided, it was not possible to pool the results of included studies. Also, [Van Tiel 2007](#) did not present the data that we needed 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 infection (i.e. major infections, minor infections and fevers of unknown origin; see [Characteristics of included studies](#) table for the exact definitions) and identified no statistically significant differences between treatment groups: 68 out of 78 participants (87%) in the cooked-diet group and 57 out of 75 (76%) in the raw-diet group developed an infection (RR 1.15, 95% CI 0.98 to 1.34; P value = 0.08; see [Figure 3](#)). Among 68 infections in the cooked-diet group were 23 major infections (34%), five minor infections (7%) and 40 fevers of unknown origin (59%). The raw-diet group had 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 were 12 microbiologically documented infections (52%), and among the 26 major infections in the raw-diet group were 22 (85%); this information was not reported for minor infections. Although not explicitly stated, we assumed that investigators performed tests to determine pathogenic organisms in all participants. Among the 23 major infections in the cooked-diet group 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 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 information was not reported for minor infections.

Figure 3. Forest plot of comparison: 1 Cooked diet vs raw diet, outcome: 1.1 Infections (i.e. major infection, minor infection and fever of unknown origin).

[Moody 2006](#) assessed the rate of neutropenic infection (see [Characteristics of included studies](#) table for the exact definition) and identified no statistically significant differences between treatment groups: 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 value = 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 four neutropenic infections (50%) in the FDA-approved

safety guidelines-only group were documented (i.e. one case of *Pseudomonas* sepsis and one of respiratory virus pneumonia).

Figure 4. Forest plot of comparison: 2 FDA food safety guidelines and neutropenic diet guidelines vs FDA food safety guidelines only, outcome: 2.1 Neutropenic infection.

Van Tiel 2007 did not report the infection rate as the number of participants with an infection (defined as a temperature $\geq 38.5^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$ with a single measurement, for which empirical antibiotics were administered), but as the number of chemotherapy cycles with infection present. As a result, we could not adequately analyse the infection rate in this study, but we have provided descriptive results: The LBD group had 14 chemotherapy cycles with infection (of which seven were microbiologically confirmed (50%)) among 20 chemotherapy cycles given (70%), and the normal hospital-diet group had 17 chemotherapy cycles with infection (of which seven were microbiologically confirmed (41%)) among 21 chemotherapy cycles given (81%). Researchers observed no significant differences (P value = 0.48, as reported in the original article). Please note that investigators assessed this outcome for all available chemotherapy cycles, but it was unclear whether they evaluated all participants within these cycles; therefore, we cannot be certain that an intention-to-treat analysis was performed.

(Infection-related) mortality

None of the included studies mentioned infection-related mortality.

Gardner 2008 stated that overall survival (no definition provided) in both treatment groups was as expected for newly diagnosed acute myeloid leukaemia and high-risk myelodysplastic syndrome; investigators observed no significant differences (P value = 0.36, as reported in the original article).

Time to first febrile episode

One study evaluated time to fever. Moody 2006 identified no significant differences in time to fever (defined as time from onset of neutropenia to start of 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 antimycotics) to (some of) the

participants 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 antimycotics (Van Tiel 2007). In the LBD group, the median number of days per chemotherapy cycle with empirical antibiotics and antimycotics was 11 days (range 0 to 22 days) and 0 days (range 0 to 9 days), respectively, whereas in the normal hospital-diet group, the median number was 14.5 days (range 0 to 28 days) and 0 days (0 to 20 days), respectively. Investigators detected no significant differences between treatment groups for duration of empirical antibiotics (P value = 0.09, as reported in the original article) or duration of empirical antimycotics (P value = 0.96, as reported in the original article). Please note that it was unclear whether this outcome was assessed in all participants; therefore, we cannot be certain that intention-to-treat analyses were performed.

Diet acceptability

One study evaluated diet acceptability (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, and seven out of nine children (78%) felt they could follow the guidelines 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 were identified between treatment groups for following the diet easily (RR 1.10, 95% CI 0.84 to 1.45; P value = 0.50) and for following the diet throughout all chemotherapy cycles (RR 0.86, 95% CI 0.58 to 1.30; P value = 0.48) (see [Figure 5](#)). Please note that it was not stated whether all participants were evaluated for this outcome, although it is likely that they were (it was stated that no participants discontinued the study). An intention-to-treat analysis was performed.

Figure 5. Forest plot of comparison: 2 FDA food safety guidelines and neutropenic diet guidelines vs FDA food safety guidelines only, outcome: 2.2 Diet acceptability.

Quality of life

One study evaluated quality of life. [Moody 2006](#) used 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 Core and Cancer Modules; no further information provided). Please note that it was not stated whether all participants were evaluated for this outcome, although it is likely that they were (it was stated that no participants discontinued the study). However, we are not certain that an intention-to-treat analysis was performed.

DISCUSSION

Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infection, which can be life-threatening. It has been argued that a low bacterial diet (LBD) can prevent infection and (infection-related) mortality in cancer patients receiving chemotherapy that causes episodes of neutropenia, but much remains unclear. This is an update of the first systematic review conducted to evaluate this important topic in both adults and children.

To adequately ascertain the efficacy of a dietary intervention, the best study design, provided that design and execution are correct, is a randomised controlled trial (RCT) in which the only difference between intervention and control groups is the diet used.

In the original version of the review, we identified three RCTs including a total of 192 participants with different types of haematological malignancies and solid tumours, in which investigators evaluated different intervention and control diets; in the update, we identified no new eligible studies. Investigators in all studies provided only a scant description of treatment regimens. In all included studies, it was standard policy to give empirical antibiotics (and sometimes also antimycotics) to (some of) the participants diagnosed with an infection. The first study ([Gardner 2008](#)) included adults and defined infection as major infections, minor infections and fevers of unknown origin. Investigators randomised participants to a diet that contained only cooked fruits and vegetables versus a diet that permitted fresh (i.e. raw) fruits and vegetables. Participants were treated in

high-efficiency particulate air-filtered rooms, and they received antimicrobial prophylaxis. Granulocyte colony-stimulating factors were used in some participants. All participants had central lines, but neither central venous catheter (CVC) care nor oral care and hygiene practices were mentioned. The second study ([Moody 2006](#)) included children and evaluated neutropenic infections. Participants were randomised between FDA-approved food safety guidelines and neutropenic diet guidelines versus FDA-approved food safety guidelines only. Granulocyte colony-stimulating factors were used in some participants. All received hygiene instructions. All participants had central lines, but CVC care was not mentioned. Use of a protective environment, antimicrobial prophylaxis and oral care was not mentioned. The third study ([Van Tiel 2007](#)) included adults and defined infection as a temperature $\geq 38.5^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, with a single measurement for which empirical antibiotics were administered. Participants were randomised between an LBD and a normal hospital diet. Use of a protective environment, granulocyte colony-stimulating factors, oral care and hygiene practices were not mentioned, but participants did receive antimicrobial prophylaxis. It was unclear whether participants had central lines; CVC care was not mentioned.

Differences in co-interventions (e.g. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors), outcome definitions used and intervention and control diets provided precluded pooling of the results of included studies. This should be kept in mind when the results of individual studies are interpreted. Also, one study did not present the data (i.e. the number of participants with an infection) that we needed to perform adequate analyses ([Van Tiel 2007](#)).

Two individual studies identified no statistically significant differences in infection rate between participants receiving intervention and control diets ([Gardner 2008](#); [Moody 2006](#)); the study that did not present the data needed for adequate analyses reported no significant differences between treatment groups in the number of chemotherapy cycles with an infection ([Van Tiel 2007](#)). Infection-related mortality was not mentioned in any of the included studies, but investigators in one study ([Gardner 2008](#)) observed no significant differences in overall survival (no definition provided) between treatment groups. One study ([Moody 2006](#)) evaluated time to fever (defined as time from onset of neutropenia to start of fever) and identified no significant differences between treatment groups. One study provided data on use of empirical

antibiotics and antimycotics apart from infection rate (Van Tiel 2007). Again, researchers identified no significant differences in duration of empirical antibiotics and antimycotics between treatment groups. One study evaluated diet acceptability (Moody 2006) and no significant differences were identified between treatment groups 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 by parent proxy report.

In this review, we tried to perform intention-to-treat analyses, because they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000). However, for assessment of infection rate and use of empirical antibiotics by Van Tiel 2007 and quality of life by Moody 2006, it was unclear whether these outcomes were assessed in all participants, 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'. It is possible that no significant differences between treatment groups were identified because participants included in these studies were too few to reveal a difference (i.e. low power). Also, baseline imbalances between treatment groups (as included in the other potential sources of bias assessment) might have played a role.

Risk of bias in included studies varied. Often, bias could not be ruled out because of lack of reporting. However, at the moment, this is the best available evidence from RCTs comparing an LBD versus a control diet.

Even though RCTs provide the highest level of evidence, it should be recognised that data from non-randomised studies are available. Trifilio 2012 compared the neutropenic diet (ND) versus a general hospital diet (GD) in participants with adult hematopoietic stem cell transplantation at one centre. As far as we are aware, this is the only non-randomised study that compared ND versus GD. Researchers analysed the electronic medical records of 726 consecutive recipients; 363 participants received ND (from October 2004 to August 2006), and the next 363 participants received GD (September 2006 to August 2008). In the GD group, significantly fewer microbiological infections were confirmed compared with the ND group. No differences between groups were detected for length of hospital stay, days to engraftment, neutropenic fever,

duration of antibiotic therapy and overall mortality. No information was given on quality of life and diet adherence, although the change to GD was received well by participants. Results of this non-randomised study seem to be in accordance with results of the three included randomised studies. The design of the study and possible confounders require caution in deriving conclusions.

We are awaiting the results of two ongoing studies (NCT00726934; NCT00947648).

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

Before definitive conclusions can be reached about the efficacy of different LBDs, additional high-quality research is needed. Future trials should be RCTs performed in homogeneous study populations (e.g. with regards to anticancer treatment received). 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. Finally, the number of participants included should be sufficient to obtain the power needed for reliable results.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gardner 2008

Methods	Randomisation performed by the Leukaemia Department Data Management Office using patients' early risk of mortality scores as a stratification factor
Participants	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% to 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
Interventions	<p>Diet that contained only cooked fruits and vegetables (n = 78) vs diet that permitted fresh (i.e. raw) fruits and vegetables (n = 75)</p> <p>Participants in the raw-diet group were instructed to eat a fresh fruit or vegetable each day</p> <p>All participants were treated in high-efficiency particulate air-filtered rooms</p> <p>All participants received antimicrobial prophylaxis with levofloxacin, valacyclovir and, depending on the 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 was provided</p> <p>All participants had central lines; CVC care was not reported</p> <p>Oral care was not reported</p> <p>Hygiene practices (including hand washing) was not reported</p> <p>Granulocyte colony-stimulating factor was used only when neutrophil recovery was delayed (i.e. by 6 weeks) or after a major infection had developed. Its use was equally infrequent in the cooked- and raw-diet groups; no further information was provided</p> <p>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 was provided</p>
Outcomes	Infections, including:

Gardner 2008 (Continued)

- major infections (defined as pneumonia, bacteraemia, fungaemia or pneumonia accompanied by bacteraemia or fungaemia);
- minor infections (no definition provided); and
- fevers of unknown origin (no definition provided).

A diagnosis of pneumonia required a compatible chest x-ray or computed tomography scan. Bronchoalveolar lavage was performed to isolate a causative organism 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 was provided)

Notes	<p>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 raw-diet group. Participants remained in study until they were discharged from the high-efficiency particulate air-filtered room to the outpatient setting, usually after return of neutrophil count to $> 500/\mu\text{L}$, or after 6 weeks for those in whom neutrophil recovery was delayed</p> <p>All participants remained on the correct diet while in the study, although some did not eat a fresh fruit or vegetable each day as suggested</p> <p>206 patients were eligible for this study, but 53 refused randomisation; they all chose the cooked fruits and vegetables diet</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that participants were randomly assigned to different treatment groups by the Leukaemia Department Data Management Office using patients' early risk of mortality scores as a stratification factor, but no further information on methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that participants were randomly assigned to different treatment groups by the Leukaemia Department Data Management Office using patients' early risk of mortality scores as a stratification factor, but no further information on methods of randomisation was provided
Blinding of patients (performance bias)	High risk	Compliance with the assigned diet was facilitated by placing notices of this diet on participants' charts and by using diaries in which participants recorded what they ate each day. As a result, participants were not blinded
Blinding of health care providers (performance bias)	High risk	Compliance with the assigned diet was facilitated by placing notices of this diet on participants' charts and by using diaries in which participants recorded what they ate each day. As a result, healthcare providers were not blinded
Blinding of outcome assessors (detection bias): infections	Unclear risk	No information on blinding of outcome assessors was provided
Incomplete outcome data (attrition bias): infections	Low risk	For all participants, the outcome of infections was assessed
Incomplete outcome data (attrition bias): overall survival	Low risk	For all participants, the outcome of overall survival was assessed

Gardner 2008 (Continued)

Selective reporting (reporting bias)	Low risk	No protocol was mentioned in the manuscript (and we did not search for it), but all expected outcomes are reported
Other bias	Unclear risk	<p>Differences between treatment groups in baseline characteristics related to outcome:</p> <ul style="list-style-type: none"> 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) 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) Other (as reported in original study): not reported

Moody 2006

Methods	Random numbering was used to assign participants to treatment groups; participants were randomised in blocks of 10, stratified by disease (i.e. leukaemia, brain tumour or sarcoma)
Participants	19 children (18 years of age or younger, 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). Participants received active treatment with myelosuppressive chemotherapy. Exclusion criteria included co-morbid immunosuppressive disease, myeloablative chemotherapy in preparation for bone marrow transplant, documented fever or infection at time of enrolment, inability to tolerate oral feeding and concurrent radiation to the central nervous system or gastrointestinal tract
Interventions	<p>Both FDA-approved food safety guidelines (Food Safety 2005) and neutropenic diet guidelines (i.e. not eating raw fruits (except 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; all produce cooked to well done, eggs must be hard-boiled) (n = 9) vs FDA-approved food safety guidelines only (n = 10)</p> <p>Participants were instructed to start to follow their diet on the first day of the chemotherapy cycle and to continue the diet until completion of the study period</p> <p>Protective environment was not reported</p> <p>Antimicrobial prophylaxis was not reported</p> <p>All patients had central lines (a Broviac/Hickman or a Port-a-Cath); CVC care was not reported</p> <p>Oral care was not reported</p> <p>Hygiene practices (including hand washing) were included in the FDA food safety guidelines, so all participants received them</p> <p>Use of colony-stimulating factors: 4 participants in the neutropenic diet group and 5 in the FDA food safety group received post-chemotherapy filgrastim</p> <p>If fever was detected, the participant was admitted to the hospital and was started on broad-spectrum antibiotics as per the standard of care; no further information was provided</p>
Outcomes	<p>Infections, including:</p> <ul style="list-style-type: none"> neutropenic infections operationalised to include febrile neutropenia defined as an oral temperature $\geq 38^{\circ}\text{C}$ as measured by parent or documented by clinic/hospital staff and an ANC $< 500 \times 10^9/\text{L}$ or

Moody 2006 (Continued)

admission to hospital and treatment with broad-spectrum antibiotics for presumed infection and an ANC $< 500 \times 10^9/L$; and

- documented infections such as positive blood, urine, stool or sputum cultures or positive radiographic evidence of infection including abscess, pneumonia or typhlitis.

Time to first fever (defined as time from onset of neutropenia to fever)

Acceptability of diet (assessed by interviewing participants and their parents qualitatively using 7 questions)

Quality of life (assessed 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](#))

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 differences). Participants were followed until neutrophil recovery (defined as ANC $> 500 \times 10^9/L$ on 2 consecutive complete blood counts)

All participants received their assigned diet and planned chemotherapy. Diet adherence rate was 94.1% in the intervention group and 99.99% in the control group

21 patients were eligible for this study, but 2 were not included: 1 refused to participate because of depression and 1 suffered from a new-onset psychosis and therefore was not approached

At baseline statistically significant differences between treatment groups were noted in history of febrile neutropenia (all participants in the neutropenic diet group vs 5 out of 10 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; study authors stated that this was most likely secondary to the small sample size)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbering was used to assign participants to treatment groups
Allocation concealment (selection bias)	Low risk	It was stated that participants' diet allocation was concealed from the investigator until after the patient had consented to participate in the study
Blinding of patients (performance bias)	Low risk	It was stated that participants and their parents were blinded to the intervention
Blinding of health care providers (performance bias)	Unclear risk	It was stated that the medical team was blinded to the intervention (so low risk of performance bias), but that the primary investigator was not. It was not clear whether the primary investigator was involved in participant care, so we cannot know for certain that the risk of performance bias was indeed low
Blinding of outcome assessors (detection bias): infections	High risk	The primary investigator assessed all infections and was not blinded
Blinding of outcome assessors (detection bias): time to first febrile episode	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessor (detection bias): diet acceptability	Unclear risk	No information on blinding of outcome assessors was provided

Moody 2006 (Continued)

Blinding of outcome assessor (detection bias): quality of life	Unclear risk	No information on blinding of outcome assessors was provided
Incomplete outcome data (attrition bias): infections	Low risk	All participants were evaluated for this outcome
Incomplete outcome data (attrition bias): time to first febrile episode	Low risk	All participants were evaluated for this outcome
Incomplete outcome data (attrition bias): diet acceptability	Unclear risk	It was not stated whether all participants were evaluated for this outcome, although it is most likely that they were (it was stated that no participants discontinued the study)
Incomplete outcome data (attrition bias): quality of life	Unclear risk	It was not stated whether all participants were evaluated for this outcome, although it is most likely that they were (it was stated that no participants discontinued the study)
Selective reporting (reporting bias)	Low risk	No protocol was mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	High risk	<p>Differences between treatment groups in baseline characteristics related to outcome:</p> <ul style="list-style-type: none"> Received anticancer treatment more likely to cause neutropenia: unclear (no large differences in types of malignancies, but stage of disease and exact treatment including doses not reported) Co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences in hygiene practices and use of colony-stimulating factors; not reported for the other items (maybe not used at all) Other (as reported in original study): a statistically significant difference in quality of life (lower in neutropenic diet group) and history of febrile neutropenia (greater in neutropenic diet group)

Van Tiel 2007

Methods	Randomisation performed by using a predetermined randomisation schedule produced by a computerised randomisation programme
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). Participants were treated with remission induction chemotherapy; no further information was provided (see notes)
Interventions	<p>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 were individually packed; yogurt desserts, soda drinks and soups were served in single-serving containers) (n = 10) vs normal hospital diet (no further information was provided) (n = 10)</p> <p>Participants started their assigned treatment as soon as possible after inclusion</p> <p>Protective environment was not reported</p>

Van Tiel 2007 (Continued)

All participants received antimicrobial prophylaxis including ciprofloxacin (500 mg every 12 hours, orally) and fluconazole (50 mg every 24 hours, orally). This was adjusted or switched to alternative drugs according to the results of surveillance cultures; no further information was provided. It was started before initiation of chemotherapy and discontinued when leucocyte counts had recovered to $\geq 1000/\text{mm}^3$

It was unclear whether participants had central lines; CVC care was not reported

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

Outcomes	<p>Infection (defined as temperature $\geq 38.5^\circ\text{C}$ or $< 36^\circ\text{C}$ with a single measurement for which empirical antibiotics were administered)</p> <p>Duration of empirical antibiotics or antimycotics (no definition provided)</p>
Notes	<p>Length of follow-up was 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 whether 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)</p> <p>All participants received their assigned diet</p> <p>Number of eligible patients not randomised was not reported</p> <p>It was not stated whether the difference in diagnoses (i.e. acute lymphoblastic leukaemia or acute myelogenous leukaemia) between treatment groups were significant. Also, the exact treatment received by participants with each diagnosis was not reported, thus making it impossible to know whether participants in 1 of the treatment groups received treatment more likely to cause neutropenia</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by using a predetermined randomisation schedule produced by a computerised randomisation programme
Allocation concealment (selection bias)	Low risk	Randomisation performed by using a predetermined randomisation schedule produced by a computerised randomisation programme
Blinding of patients (performance bias)	Unclear risk	No information on blinding of participants was provided
Blinding of health care providers (performance bias)	Unclear risk	No information on blinding of healthcare providers was provided
Blinding of outcome assessors (detection bias): infections	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	Unclear risk	No information on blinding of outcome assessors was provided
Incomplete outcome data (attrition bias): infections	Unclear risk	This outcome was assessed in all available chemotherapy cycles, but it was unclear whether all participants were evaluated within these cycles

Van Tiel 2007 (Continued)

Incomplete outcome data (attrition bias): duration of empirical antibiotics and antimycotics	Unclear risk	Unclear whether this outcome was assessed in all participants
Selective reporting (reporting bias)	Low risk	No protocol was mentioned in the manuscript (and we did not search for it), but all expected outcomes were reported
Other bias	Unclear risk	Differences between treatment groups in baseline characteristics related to outcome: <ul style="list-style-type: none"> Received anticancer treatment more likely to cause neutropenia: unclear (differences in types of malignancies were noted, but it was not reported whether this was statistically significant; stage of disease and exact treatment including doses were not reported) Co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences in antimicrobial prophylaxis use; not reported for the other items (maybe not used at all) Other (as reported in original study): not reported

ANC: absolute neutrophil count; CVC: central venous catheter; FDA: Food and Drug Administration; LBD: low bacterial diet; n: number.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brown 2014	No RCT; questionnaire paediatric oncologists
Carr 2014	No RCT; questionnaire dieticians
DeMille 2006	No RCT; no control group
Fopp 1975	No randomisation of LBD vs a control diet
Foster 2014	Review
Fox 2012	No RCT; review
Lund 2014	No RCT; manufacturing of LBD products
Trifilio 2012	No RCT
Veber 2010	No RCT; infection not evaluated
Wilson 2002	No RCT; review
Ziegler 1992	No evaluation of an LBD vs control treatment

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

Characteristics of studies awaiting assessment [ordered by study ID]

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 vs standard hospital food (numbers per group not reported). All participants received partial protective isolation and selective gastrointestinal decontamination
Outcomes	<p>42 children had 55 episodes (29 episodes in cooked-food group and 26 episodes in standard hospital-food group) of ≥ 10 days with granulocyte counts $< 500/\mu\text{L}$</p> <p>Cooked-food diet (637 study days):</p> <ul style="list-style-type: none"> 3 septicaemias, 2 major infections, 2 minor infections and 5 episodes of fever of unknown origin; no deaths from infection; number of infections per 1000 days at risk (i.e. granulocytes $< 500/\mu\text{L}$): 11.0 days; and number of febrile episodes per 1000 days at risk (i.e. granulocytes $< 500/\mu\text{L}$): 7.8 days. <p>Standard hospital-food diet (925 study days):</p> <ul style="list-style-type: none"> 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 $< 500/\mu\text{L}$): 15.1 days; number of febrile episodes per 1000 days at risk (i.e. granulocytes $< 500/\mu\text{L}$): 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 treatment groups; and for all other outcomes, no level of significance for the difference was mentioned. <p>No definitions of the outcomes mentioned were provided</p>
Notes	This study has not been published in full text (checked 4 May 2015); the information provided here is based on a conference abstract in the 1997 edition of the Annual Meeting of the American Society of Hematology and on additional information provided by study authors (i.e. from the abstract, it was not clear whether participants were children; however, study authors were able to confirm that participants were indeed children; exact age range was not provided). From currently available data, it is unclear whether this study fulfils all inclusion criteria for this review

RCT: randomised controlled trial.

Characteristics of ongoing studies [ordered by study ID]

NCT00726934

Trial name or title	Effectiveness of the neutropenic diet in paediatric oncology patients
Methods	Method of randomisation not clear
Participants	Patients (1 to 30 years of age) 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) vs FDA-approved food safety guidelines
Outcomes	Neutropenic infection, documented infection and quality of life

NCT00726934 (Continued)

Starting date	September 2007
Contact information	Principal investigator: Karen Moody
Notes	No full-text publication was available as of 4 May 2015

NCT00947648

Trial name or title	Are neutropenic diets beneficial to improve outcome?
Methods	Method of randomisation not clear
Participants	Patients (18 years of age or older) with acute myelogenous leukaemia, acute lymphocytic leukaemia or myelodysplastic syndrome who will be receiving myelosuppressive chemotherapy
Interventions	Raw diet (i.e. cooked food and raw fruits and vegetables) vs cooked diet (i.e. standard neutropenic diet with only cooked food)
Outcomes	Infection rate, incidence of fever requiring intravenous antibiotics and death rate
Starting date	July 2009
Contact information	Principal investigator: Alison Gardner
Notes	No full-text publication was available as of 4 May 2015

FDA: Food and Drug Administration.

DATA AND ANALYSES

Comparison 1. Cooked diet versus raw diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infections (i.e. major infection, minor infection and fever of unknown origin)	1	153	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.98, 1.34]

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

Study or subgroup	Cooked diet n/N	Raw diet n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gardner 2008	68/78	57/75		100%	1.15[0.98,1.34]
Total (95% CI)	78	75		100%	1.15[0.98,1.34]
Total events: 68 (Cooked diet), 57 (Raw diet)					
Cooked diet 0.01 0.1 1 10 100 Raw diet

Comparison 2. FDA food safety guidelines and neutropenic diet guidelines versus FDA food safety guidelines only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neutropenic infection	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.39, 3.19]
2 Diet acceptability	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Diet was easy to follow	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.84, 1.45]
2.2 Able to follow diet throughout all chemotherapy cycles	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.30]

Analysis 2.1. Comparison 2 FDA food safety guidelines and neutropenic diet guidelines versus FDA food safety guidelines only, Outcome 1 Neutropenic infection.

Analysis 2.2. Comparison 2 FDA food safety guidelines and neutropenic diet guidelines versus FDA food safety guidelines only, Outcome 2 Diet acceptability.

APPENDICES

Appendix 1. 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, October 2011, and May 2015:

- 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]

Appendix 2. 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] OR granulocytopeni*[tiab] OR immunocompromized[tiab] OR immunocompromised[tiab] AND ((sterile[tiab] OR clean[tiab] OR low bacteria*[tiab] OR low microb*[tiab] OR minimal bacteria*[tiab] OR minimal microb*[tiab] OR germ poor[tiab] OR cooked[tiab] OR reduced bacteria*[tiab]) AND (diet[mesh] OR diet[tw] OR feeding[tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition[tiab] OR dietary restriction*[tiab])

[tw = text word; tiab = title or abstract; mesh = medical subject heading; * = zero or more characters]

Appendix 3. 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]

Appendix 4. CINAHL search strategy

S1 AB 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\$

S2 TI 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\$

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 immunocompromized 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 immunocompromized 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, October 2011, and May 2015:

S1 AB 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\$
S2 TI 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\$
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 immunocompromized 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 immunocompromized 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 S14 or S15
S17 S16 or S9
S18 S17 and S13

[AB = abstract; TI = title; MH = exact subject heading; \$ = zero or more characters; + = explosion]

Appendix 5. Ongoing trial registers and conference proceedings search strategies

We have searched the register of the National Institutes of Health (www.clinicaltrials.gov) and ISRCTN register (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.

WHAT'S NEW

Date	Event	Description
16 April 2019	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 9, 2012

Date	Event	Description
17 December 2015	New citation required but conclusions have not changed	No new studies were identified during the update. Thus the conclusions have not changed
4 May 2015	New search has been performed	The search for eligible studies was updated to May 2015
29 January 2015	Amended	Contact details were updated

CONTRIBUTIONS OF AUTHORS

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

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

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

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

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

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

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

All authors approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

While performing the review, review authors adapted some of the information provided in the protocol: In the protocol, we stated that patients with compromised immune systems (acquired or congenital, or patients with cancer) who are likely to receive chemotherapy causing episodes of neutropenia were eligible for inclusion. However, we focused the review on oncology patients only. Furthermore, to avoid missing potentially relevant information, we changed the definition of the control intervention from "no low bacterial diet" to "any other diet", and we changed the rather strict definitions of our outcome measures to "as defined by the authors of the original study". We expanded our search: We added ongoing trials databases, and we added an additional conference (i.e. Oncology Nurses Society). Also, we improved the search strategy for the CENTRAL, DARE and CINAHL databases. Since our protocol was developed, the 'Risk of bias' criteria used by The Cochrane Collaboration have changed; we used the most recent version for our review. In addition, we included assessment of reporting bias by constructing a funnel plot when we identified a sufficient number of included studies. Pooling of results was not possible, so this was not applicable to this version of the review, but it might become relevant when the review is updated.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Antifungal Agents [therapeutic use]; Antineoplastic Agents [*adverse effects]; Bacterial Infections [*prevention & control]; Fever [diet therapy]; Mycoses [*prevention & control]; Neoplasms [*drug therapy]; Neutropenia [chemically induced] [*diet therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans