

Prevention of Infection
Systematic Reviews / Meta-analysis Table

Review Author	Study Information	Conclusions and Implications
Meta-analyses and Reviews of Pharmacologic Interventions for the Prevention of Infection in Patients With Cancer		
PEP Weight of Evidence Category: Recommended for Practice		
<p>Bohlius, 2008</p>	<p>Search strategy: The Cochrane Library, MEDLINE, EMBASE, CANCELIT, and other relevant literature databases; internet databases of ongoing trials; and conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology (1980–2007); full-text and abstract publications as well as unpublished data were included. The search covered the time period from January, 1980 to April 21, 2008.</p> <p>Sample: 13 randomized, controlled trials (RCTs), including 2,607 adult patients with malignant non-Hodgkin's or Hodgkin's lymphoma undergoing chemotherapy. All chemotherapy regimens applied were CHOP or MOPP-like and were moderately myelosuppressive.</p> <p>Treatment evaluated: Prophylaxis with granulocyte–colony-stimulating factor (G-CSF) or granulocyte macrophage–colony-stimulating factor (GM-CSF) within 48 hours after chemotherapy versus placebo or no prophylaxis. Eleven studies evaluated G-CSF prophylaxis and 2 studies evaluated GM-CSF prophylaxis.</p> <p>Outcomes measured: Primary outcomes</p> <ul style="list-style-type: none"> • overall survival • freedom from treatment failure <p>Secondary outcomes</p> <ul style="list-style-type: none"> • quality of life • risk and duration of neutropenia • risk and duration of febrile neutropenia • infection • mortality during chemotherapy • received dose intensity of chemotherapy • tumor response (complete response) • adverse effects of G-CSF and GM-CSF • risk and duration of parenteral antibiotic treatment • hospitalization • risk and duration of thrombocytopenia and anemia 	<p>In adult patients with malignant lymphoma undergoing chemotherapy, G-CSF or GM-CSF did <i>not</i> affect:</p> <ul style="list-style-type: none"> ▪ Overall survival ▪ Overall mortality ▪ Infection-related mortality ▪ Freedom from treatment failure ▪ Complete tumor response ▪ Quality of life ▪ Thrombocytopenia ▪ Anemia ▪ The need for parenteral antibiotics <p>G-CSF or GM-CSF significantly reduced:</p> <ul style="list-style-type: none"> ▪ The risk of neutropenia (absolute neutrophil count [ANC] < 500) by 33% ▪ The risk of febrile neutropenia (ANC < 500) by 41% (Data only were available for G-CSF.) ▪ The risk of febrile neutropenia (ANC < 1000) by 26% (Data only were available for G-CSF.) ▪ The risk of infection by 26%. <p>No evidence was conclusive that G-CSF or GM-CSF shortens the duration of neutropenia, febrile neutropenia, hospitalization, or duration of parenteral antibiotic treatment.</p> <p>In three studies, patients in the G-CSF or GM-CSF treated groups received statistically significant higher dose intensity than the control group.</p> <p>Adverse effects: The risk of bone pain for patients treated with G-CSF or GM-CSF was more than doubled, compared to the control group (RR 3.57; 95% CI 2.09 to 6.12). The risk of an injection site reaction for patients treated with G-CSF or GM-CSF was increased more than fivefold (RR 6.55; 95%CI 3.01 to 14.25).</p>
<p>Bow et al., 2002</p>	<p>Search strategy: MEDLINE and EMBASE (1966–2000); additional studies were identified from bibliographies of articles, topical reviews, and information from the pharmaceutical industry and investigators in the field.</p>	<p>In severely neutropenic patients (ANC < 1,000 for a week or more), antifungal prophylaxis reduced the use of</p> <ul style="list-style-type: none"> ▪ Parenteral antifungal therapy by 43% (prophylaxis success) ▪ Superficial fungal infection by 71%

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	<p>Sample: 38 RCTs, including 7,014 patients who received cytotoxic therapy for acute leukemia or hematopoietic stem cell transplantation (HSCT) sufficient to result in neutropenia (ANC < 1000) lasting one week or more</p> <p>Treatment evaluated: antifungal prophylaxis with azoles (fluconazole, itraconazole, ketoconazole, and miconazole) or an amphotericin B formulation compared with placebo or no prophylaxis controls</p> <p>Outcomes measured: prophylaxis success (study completion without the administration of parenteral, full-dose antifungal therapy for patients with suspected or proven fungal infection), superficial fungal infection (infections of the integumentary surfaces), proven invasive fungal infection (microbiologic or histologic identification of a fungal pathogen from a normally sterile body site in association with clinical evidence of infection), overall mortality, fungal infection-related mortality, incidence of invasive aspergillosis (proven fungal infection attributable to <i>Aspergillus</i> spp.)</p>	<ul style="list-style-type: none"> ▪ Invasive fungal infection by 56% ▪ Fungal infection-related mortality by 42%. <p>In subgroup analyses, superficial fungal infections were not reduced for</p> <ul style="list-style-type: none"> ▪ HSCT recipients overall ▪ Patients receiving low-dose amphotericin B formulations ▪ Patients in a single, small miconazole trial. <p>However, superficial fungal infections were reduced in HSCT recipients on azoles.</p> <p>In subgroup analyses, fluconazole was more effective than itraconazole or low-dose amphotericin B formulations to prevent superficial fungal infections.</p> <p>In subgroup analyses, a reduction in fungal infection-related mortality was not observed in</p> <ul style="list-style-type: none"> ▪ Pediatric trials ▪ Non-HSCT trials ▪ Trials comparing azoles with polyene controls ▪ Trials comparing low-dose amphotericin B formulations with placebo ▪ Trials with itraconazole, ketoconazole, or miconazole. <p>There was a reduction in fungal infection-related mortality in trials using fluconazole for antifungal prophylaxis.</p> <p>Antifungal prophylaxis did not affect</p> <ul style="list-style-type: none"> ▪ Overall mortality except in subsets of HSCT recipients or patients in which the mean duration of neutropenia was longer than two weeks ▪ The incidence of aspergillosis, perhaps because the overall incidence was low (1%) in both groups; therefore, a treatment effect could not be detected.
Clarkson, 2007	<p>Search strategy: The methodology used was developed by the Cochrane collaboration. Electronic databases searched included Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE pre-indexed, EMBASE, CINAHL, CANCERLIT, SIGLE, and LILACS. The most recent search was June 2006. The reference list of related review articles and all articles obtained were checked for further trials. Authors of trial reports and specialists in the field known to the review authors were written to concerning further published and unpublished trials.</p> <p>Sample: 28 RCTs involving 4,226 patients who had received chemotherapy and/or radiotherapy. 17 of the 28 trials recruited only adult patients with cancer, 8 included adults and children, and 2 included children only; in one trial, the age of the patients was unclear. The type of cancer being treated was leukemia in 18 trials, solid tumors in 3 trials, and a combination of both in 7</p>	<p>Drugs absorbed and partially absorbed from the gastrointestinal (GI) tract were found to prevent oral candidiasis when compared to a placebo, or a no treatment control group, with RR for absorbed drugs = 0.47 (95% confidence interval (CI) 0.29 to 0.78).</p> <p>For absorbed drugs in populations with an incidence of 20% (mid-range of results in control groups), this implies that 9 (95% CI 7 to 13) patients need to be treated to avoid one patient getting oral candidiasis.</p> <p>There was no significant benefit shown for drugs not absorbed from the GI tract. Therefore, there is strong evidence that some antifungal drugs prevent oral candidiasis (thrush) caused by cancer treatment, but nystatin does not appear to work.</p> <p>Absorbed from the GI tract</p> <ul style="list-style-type: none"> • Fluconazole • Ketoconazole • Itraconazole <p>Partially absorbed from the GI tract</p> <ul style="list-style-type: none"> • Miconazole

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	<p>trials.</p> <p>Treatment evaluated: Active agents: any antifungal intervention (partially absorbed, fully absorbed, and nonabsorbable oral or topical antifungals) for the prevention of oral candidiasis Control: placebo or no treatment, or another active intervention</p> <p>Outcomes measured: prevention of oral candidiasis</p>	<ul style="list-style-type: none"> • Clotrimazole • Amphotericin B • Nystatin • Chlorhexidine • Nystatin + chlorhexidine • Thymostimulin • Amphotericin B + nystatin • Polyenes (amphotericin B or nystatin) • Natamycin • Norfloxacin + amphotericin B <p>Not absorbed from the GI tract</p> <p>The percentage of patients developing candidiasis in the 19 control or no treatment groups ranged from 5% to 100%, with a median value of 50%.</p> <p>Seven trials involving 1,153 patients compared drugs absorbed from the GI tract with placebo, or 'no treatment' control group and the meta-analysis showed that these drugs prevented oral candidiasis with risk ratio (RR) of 0.47 (95% confidence interval (CI) 0.29 to 0.78, P = 0.12).</p> <p>Four trials involving 292 patients compared drugs partially absorbed from the GI tract with placebo and these drugs were also found to prevent oral candidiasis (RR = 0.13, 95% CI 0.06 to 0.46, P = 0.15).</p> <p>Eight studies involving 382 patients compared drugs not absorbed from the GI tract with placebo or no treatment control groups, and overall the drugs did not have a significant benefit in preventing oral candidiasis (RR = 0.68 (95% CI 0.46 to 1.02, P < 0.001).</p> <p>Eight studies compared drugs absorbed from the gastrointestinal tract directly with those not absorbed. The meta-analysis showed a significant benefit in using the absorbed drugs rather than those not absorbed to prevent oral candidiasis (RR = 0.40, 95% CI 0.21 to 0.76, P = 0.052).</p>
<p>Cornely et al., 2003</p>	<p>Search strategy: not described</p> <p>Sample: 38 RCTs of primary antifungal prophylaxis and 13 historically controlled or uncontrolled trials of primary antifungal prophylaxis, including more than 9,000 neutropenic patients with hematologic malignancies</p> <p>Treatment evaluated: primary antifungal prophylaxis with fluconazole, itraconazole, or an amphotericin B product in neutropenic patients with hematologic malignancies</p> <p>Outcomes measured: not described</p> <p>Systematic review of the literature with evidence ranking using the Infectious</p>	<p>Recommended antifungal prophylactic regimens for patients with hematologic malignancies and their level of evidence:</p> <p><u>Conventional chemotherapy</u> Fluconazole 50–400 mg every day by mouth (CI) Itraconazole oral suspension 5 mg/kg every day (BI) Amphotericin B desoxycholate 1.0 mg/kg every 48 hour by IV (CII) Amphotericin B desoxycholate 20 mg inhalation (CI)</p> <p><u>Allogeneic transplantation</u> Fluconazole 400 mg every day by mouth (AI) Fluconazole 50–200 mg every day by mouth (CI)</p>

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	<p>Diseases Society of America (IDSA) and U.S. Public Health Service grading system</p> <p>IDSA–U.S. Public Health Service Grading System for ranking recommendations in clinical guidelines</p> <p><i>Strength of recommendation:</i></p> <ul style="list-style-type: none"> • A: good evidence to support a recommendation for use • B: moderate evidence to support a recommendation for use • C: poor evidence to support a recommendation for use • D: moderate evidence to support a recommendation against use • E: good evidence to support a recommendation against use <p><i>Quality of evidence:</i></p> <ul style="list-style-type: none"> • I: evidence from ≥ 1 properly randomized, controlled trial • II: evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments • III: evidence from opinions of respected authorities; based on clinical experience, descriptive studies, or reports of expert committees 	<p>Liposomal amphotericin B 1.0 mg/kg every day by IV (CI)</p>
<p>Cruciani et al., 2003</p>	<p>Search strategy: Medline, CancerLit, Database of Abstracts of Reviews of Effects, and Cochrane Library (1984–2002); the bibliographies of retrieved studies also were reviewed.</p> <p>Sample: 9 RCTs with 1,202 neutropenic patients with cancer</p> <p>Treatment evaluated: prophylaxis with a fluoroquinolone (ciprofloxacin, ofloxacin, perfloxacin or norfloxacin) in combination with an antibiotic against gram-positive bacteria (penicillins, macrolide, rifampin, or vancomycin) compared to fluoroquinolone alone in neutropenic patients with cancer</p> <p>Outcomes measured: bacteremic episodes, gram-positive infections, gram-negative infections, clinically documented infections, mortality, febrile morbidity, and side effects related to prophylaxis</p>	<p>The addition of gram-positive prophylaxis to fluoroquinolones reduced</p> <ul style="list-style-type: none"> ▪ Total episodes of bacteremia by 11.1% ▪ Staphylococcal and streptococcal infections ▪ Febrile morbidity by 6.7%. <p>No difference was found between gram-positive prophylaxis and a fluoroquinolone compared with a fluoroquinolone alone with regard to</p> <ul style="list-style-type: none"> ▪ Clinically documented infections ▪ Gram-negative infections ▪ Unexplained episodes of fever ▪ Infectious mortality. <p>However, adding gram-positive prophylaxis significantly increased the occurrence of side effects, primarily gastrointestinal intolerance and liver function test abnormalities seen with rifampin and roxithromycin.</p> <p>The authors concluded that the evidence does not support routine use of gram-positive coverage in combination with a fluoroquinolone for antibacterial prophylaxis in neutropenic patients with cancer.</p>
<p>Cruciani et al., 1996</p>	<p>Search strategy: MEDLINE was searched for literature published from January 1984–October 1994. Key words used in the search were</p>	<p>Prophylaxis with fluoroquinolones alone was shown to significantly reduce the frequency of gram-negative bacteremia. No significant difference was found in terms of gram-positive bacteremia or</p>

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	<p>neutropenia/agranulocytosis and bacterial infections. <i>Current Contents</i> also was used, as were the bibliographies from MEDLINE articles.</p> <p>Criteria: Eligible studies were randomized, controlled trials with fluoroquinolones alone or in combination with gram-positive prophylaxis in granulocytopenic patients receiving chemotherapy for cancer.</p> <p>Sample: 19 studies were included in the analysis, with the majority of patients having hematologic malignancies. Patients with solid tumor were included in six of the studies.</p> <p>Outcomes measured: Prevention of infection was evaluated by comparing infection-related morbidity and mortality, as well as rates of bacteremia and fever.</p>	<p>infection-related mortality.</p> <p>Fluoroquinolone with gram-positive prophylaxis significantly reduced the frequency of gram-positive bacteremia. Fever-related morbidity and infection-related mortality were not affected. Of note, the majority of the studies (4 of 6) used fluoroquinolone alone in the control group.</p>
<p>Engels et al., 1998</p>	<p>Search strategy: MEDLINE (1966–1996); the reference lists of retrieved articles also were reviewed.</p> <p>Sample: 18 RCTs with 707 patients undergoing chemotherapy for malignancy (primarily hematologic malignancies)</p> <p>Treatment evaluated: Quinolone prophylaxis compared with placebo (9 trials) or trimethoprim-sulfamethoxazole (9 trials). The article did not state whether patients received G-CSFs.</p> <p>Outcomes measured: incidence of fevers, gram-negative infections and bacteremias, gram-positive infections and bacteremias, disseminated fungal infections, total microbiologically documented infections, total infections, and infection-related deaths</p>	<p>Without prophylaxis</p> <ul style="list-style-type: none"> ▪ 82% of patients developed fever. ▪ 25% of patients developed gram-negative infections. ▪ 23% of patients developed gram-positive infections. ▪ 55% of patients developed any infection. <p>Compared with no prophylaxis, quinolone prophylaxis decreased the risk of</p> <ul style="list-style-type: none"> ▪ Gram-negative infections by 79% ▪ Gram-negative bacteremia by 77% ▪ Microbiologically documented infections by 35% ▪ Total infections by 46% ▪ Fever by 15%. <p>Compared with trimethoprim-sulfamethoxazole prophylaxis, quinolone prophylaxis decreased the risk of</p> <ul style="list-style-type: none"> ▪ Gram-negative infections by 70% ▪ Gram-negative bacteremia by 68% ▪ Microbiologically documented infections by 28% ▪ Total infections by 17%. <p>Quinolone prophylaxis did not affect the rate of</p> <ul style="list-style-type: none"> ▪ Gram-positive infection or bacteremia ▪ Fungal infection ▪ Clinically documented infection ▪ Infection-related death. <p>The rate of quinolone-resistant gram-negative infections was 3.0% and the rate of quinolone-resistant gram-positive infections was 9.4% among patients who received quinolone prophylaxis, but no data were provided regarding the rate of quinolone-resistant infections among the control group.</p>

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		Therefore, the effect of quinolone prophylaxis on the rate of quinolone-resistant infections is unknown.
Gafter-Gvili et al., 2007	<p>Search strategy: Cochrane Cancer Network Register of Trials (December 2004), Cochrane Library (Issue 4, 2004), EMBASE (January 1980–December 2004), and MEDLINE (January 1966–December 2004); the reference lists of all the articles also were searched.</p> <p>Sample: 95 RCTs, including 9,283 patients comparing prophylactic antibiotics with placebo, no intervention, or other prophylactic antibiotics; 64 trials included only patients with hematologic malignancies, and 9 trials consisted of more than 80% of patients with solid tumors. 27 studies included patients undergoing bone marrow transplantation (BMT).</p> <p>Treatment evaluated: antibiotic prophylaxis compared with placebo or no intervention or another antibiotic in afebrile neutropenic patients</p> <p>Outcomes measured: overall mortality, infection-related death, febrile episodes, clinically documented infection, microbiologically documented infection, bacteremia, adverse effects, and emergence of resistant bacteria</p>	<p>Prophylactic antibiotics significantly decreased</p> <ul style="list-style-type: none"> ▪ Overall mortality by 33%, although the effect was less robust in the well-designed trials ▪ The risk of infection-related death by 42% ▪ Fever by 21% ▪ Clinically documented infections by 36% ▪ Microbiologically documented infections by 46% ▪ Gram-negative infections by 61% ▪ Gram-positive infections by 58% ▪ Bacteremia by 48%. <p>Fluoroquinolones, when compared with placebo or no intervention, decreased the risk of</p> <ul style="list-style-type: none"> • Overall mortality compared with placebo or no intervention by 48% • Infection-related mortality by 62% • Clinically documented infections by 47% • Microbiologically documented infections by 50% • Gram-negative infections by 74% • Gram-positive infections by 71% • Bacteremia by 36%. <p>The relative risk for adverse events was not statistically significant (relative risk 1.30 [confidence interval 0.61–2.76]). Comparatively, in trials comparing trimethoprim-sulfamethoxazole with placebo or no intervention, the corresponding estimates were statistically significant (relative risk 2.42 [confidence interval 1.35–4.36] and 3.63 [confidence interval 1.32–9.98], respectively). Moreover, in trials that compared fluoroquinolones with trimethoprim-sulfamethoxazole, less resistance developed to fluoroquinolones in the fluoroquinolone group than that developed to trimethoprim-sulfamethoxazole in the trimethoprim-sulfamethoxazole group (relative risk 0.45 [confidence interval 0.27–0.74]). When fluoroquinolones were compared with placebo, the number of fungal infection episodes did not statistically or significantly differ (relative risk 0.83 [confidence interval 0.56–1.22]).</p> <p>Fluoroquinolone prophylaxis increased the risk of fluoroquinolone-resistant infections, but the increased risk was not statistically significant (relative risk 1.69 [confidence interval 0.73–3.92]).</p>
Gafter-Gvili, et al.(2005)	<p>Search strategy: Electronic searches on The Cochrane Cancer Network Register of Trials (2005), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2005), MEDLINE (1966 to 2005) and EMBASE (1980 to 2005) and abstracts of conference proceedings; references of identified studies; the first author of each included trial was contacted.</p>	<ul style="list-style-type: none"> • Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no intervention (RR 0.66 [95%CI 0.55 to 0.79]). The authors estimated the number needed to treat (NNT) in order to prevent 1 death from all causes as 50 (95% CI 34 to 268). • Prophylaxis with any antibiotic resulted in a significant decrease in the risk of infection-related death, RR 0.59 (95% CI 0.47 to 0.75) and in the occurrence of fever, RR 0.77 (95% CI 0.74 to 0.81) • Quinolone prophylaxis reduced the risk for all-cause mortality, RR 0.52 (95% CI, 0.37 to

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	<p>Sample: One-hundred and one RCTs or quasi-RCTs including 12,599 patients with cancer and neutropenia as a result of chemotherapy or bone marrow transplantation performed between the years 1973 to 2005</p> <p>Treatment evaluated: antibiotic prophylaxis compared with placebo, no intervention, or another antibiotic to prevent bacterial infections in afebrile neutropenic patients.</p> <p>Outcomes measured: Primary outcome measures • Mortality at 30 day follow-up or at the end of the follow up in each study • Number of patients that developed febrile episodes, number of days of fever Secondary outcome measures • Clinically documented infection, defined as the presence of symptoms or signs of inflammation at an anatomic site whether pathogens were recovered from the affected site or not • Microbiologically documented infection, defined as the presence of symptoms or signs of inflammation at an anatomic site when pathogens were recovered from the affected site • Types of bacteria grown in cultures from patients with febrile episodes (Gram-positive or Gram-negative bacteria) • Episodes of bacteremia, defined as the recovery of bacteria from one or more blood cultures • Number of patients who developed super-infection or bacteria resistant to the given antibiotic in at least one of the follow-up cultures • Number of people that were admitted to the hospital and length of hospital stay Adverse events</p> <p>Limitations: Most studies were limited to hematological cancer patients (mostly leukemia). Most were conducted on hospitalized patients. Information on all cause mortality could not be obtained for all the studies. Many studies were dated.</p>	<p>0.74) and the risk of infection-related mortality, RR 0.49 (95% CI 0.31 to 0.77).</p> <ul style="list-style-type: none"> • Antibiotic prophylaxis resulted in a significant decrease in the occurrence of clinically documented infection, RR 0.66 (95% CI 0.61 to 0.73). • Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented infection, RR 0.53 (95% CI 0.48 to 0.58). • Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented Gram-negative infection, RR 0.38 (95% CI 0.32 to 0.45). • Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented Gram- positive infection, RR 0.44 (95% CI 0.38 to 0.51). • Antibiotic prophylaxis resulted in a significant decrease in the occurrence of bacteremia, RR 0.52 (95% CI 0.47 to 0.59). • Quinolone prophylaxis reduced the risk of bacteremia, RR 0.58 (95% CI 0.50 to 0.68). • When compared to placebo or no intervention, all prophylactic antibiotics caused more side effects, RR 1.59 (95% CI 1.37 to 1.85). • There was no statistically significant difference in the number of episodes of fungal infection when prophylactic antibiotics were compared to placebo, RR 1.07 (95% CI 0.83 to 1.37, 38 studies, 2682 participants) • When compared to placebo, patients given quinolones and TMP-SMZ were found to be at increased risk of harboring bacilli resistant to the specific drug than patients receiving placebo, RR 1.47 (95% CI 1.08 to 2.01). For quinolones the RR was 1.18 (95% CI 0.81 to 1.70) and for TMP-SMZ 2.42 (95% CI 1.35 to 4.36) • When quinolones were compared to TMP-SMZ microbiologically documented infections were significantly reduced, RR 0.72 (95%CI 0.6 to 0.86) (comparison 5.2), Gram-negative infections, RR 0.21 (95% CI 0.13 to 0.36) (comparison 6.2), Gram-negative bacteremia, RR 0.35 (95% CI 0.21 to 0.59) and side effects RR 0.74 (95%CI 0.63 to 0.87). • The addition of antibiotic against gram-positive infection to quinolones resulted in a significant decrease in the number of bacteremic episodes, RR 0.72 (95%CI 0.57 to 0.92), Gram-positive infections, RR 0.49 (95% CI 0.37 to 0.64), and Gram-positive bacteremia, RR 0.61(95% CI 0.45 to 0.83), but also in more side effects.
<p>Gafter-Gvili, Paul, Fraser, & Leibovici, 2007)</p>	<p>Search strategy: Relevant trials were identified from electronic searches of Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006), MEDLINE (1966-6/2006), EMBASE (1980–2005), and the following conference proceedings: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (1995–2004), Annual Meetings of the Infectious</p>	<ul style="list-style-type: none"> • Primary outcome. <ul style="list-style-type: none"> ○ Of the 22 trials comparing quinolones with placebo or no intervention, only three trials reported on colonization by resistant organisms at the end of follow-up. Compared with placebo or no intervention, there was a statistically non-significant increase in the rate of colonization by quinolone-resistant organisms with prophylaxis at the end of the study (RR 1.68; 95% CI 0.71–4.0).

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	<p>Diseases Society of America (IDSA) (2001–2004), and the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) (2001–2006) and hand searches of references from relevant publications. No language restriction was set.</p> <p>Sample: 56 trials which randomized 7878 patients. Twenty-two compared quinolones with placebo or no Treatment and 34 compared quinolones with other antibiotics: quinolones versus trimethoprim/sulfamethoxazole in 11 trials, quinolones versus non-absorbable antibiotics in 8 trials, quinolones versus fluoroquinolones with additional antibiotics for coverage against Gram-positive infections in 8 trials, quinolones plus trimethoprim/sulfamethoxazole versus trimethoprim/sulfamethoxazole in 2 trials, and quinolones versus other quinolones in 5 trials. The trials were published between 1987 and 2005. Most trials included patients with hematological malignancies or undergoing bone marrow transplantation (48 trials). In most trials the patients were hospitalized throughout the duration of antibiotic prophylaxis.</p> <p>Treatment evaluated: Randomized or quasi-randomized controlled trials comparing quinolone prophylaxis with placebo or no intervention, or with another antibiotic, for the prevention of bacterial infections in afebrile neutropenic patients.</p> <p>Outcomes measured: The primary outcomes assessed were: (i) rates of colonization with quinolone-resistant bacteria (ii) microbiologically documented infections caused by quinolone-resistant bacteria.</p>	<ul style="list-style-type: none"> ○ There was no difference in the proportion of patients who developed infections caused by bacteria resistant to quinolones (RR 1.04; 95% CI 0.73–1.5) (8 trials). ○ Of the 154 episodes of microbiologically documented infections in the quinolone arm, 54 were caused by quinolone-resistant organisms (30%) versus 51/308 (16%) without prophylaxis. ○ There was no difference in the number of patients who developed infections caused by quinolone-resistant Gram-negative bacteria (RR 1.3; 95% CI 0.63–2.67) or by quinolone-resistant Gram-positive bacteria (RR 0.93; 95% CI; 0.61–1.42) in the quinolone arm versus placebo/no treatment. ● Conclusion: The absolute rate of quinolone-resistant infections is not significantly increased in patients receiving quinolone prophylaxis overall, however, when infections do develop, 1/3 of infections are resistant to the administered quinolone; thus, quinolones should not be given as empirical treatment to patients following quinolone prophylaxis. ● This meta-analysis was limited by the small number of trials reporting resistant infections.
<p>Glasmacher et al., 2003</p>	<p>Search strategy: Cochrane Central Register of Controlled Trials and MEDLINE (1966–July 2003); abstracts from the annual meetings of the American Society of Hematology, Interscience Conference on Antimicrobial Agents and Chemotherapy, European Hematology Association, European Group for Blood and Marrow Transplantation, German and Austrian Society of Hematology and Oncology, and the British Society for Hematology were screened from 1994–2003. Reference lists of relevant studies were reviewed. The pharmaceutical manufacturer of itraconazole was contacted.</p> <p>Sample: 13 RCTs involving 3,597 patients, 1,812 on itraconazole and 1,785 controls, with hematologic malignancies who were neutropenic (ANC < 500) following chemotherapy or BMT</p> <p>Treatment evaluated: itraconazole solution or capsules compared with</p>	<ul style="list-style-type: none"> ● A statistically significant decrease was found in the incidence of invasive fungal infections in the itraconazole solution group (49% reduction) but not the itraconazole capsule group ● A statistically significant decrease existed in the incidence of invasive yeast infections in the itraconazole solution group (60% reduction) but not the itraconazole capsule group ● A statistically significant decrease was found in the incidence of proven invasive Aspergillus infections in the itraconazole solution group (48% reduction) but not the itraconazole capsule group ● A statistically significant decrease was noted regarding mortality in the itraconazole solution group (42% reduction) but not the itraconazole capsule group. ● No significant difference existed between the groups regarding mortality from any cause during the study period. <p>Antifungal prophylaxis with an itraconazole solution for neutropenic patients with hematologic</p>

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	<p>control (no treatment, placebo, oral polyenes, or fluconazole)</p> <p>Outcomes measured: incidence of invasive fungal infections, invasive yeast infections, proven invasive Aspergillus infections, mortality from proven invasive fungal infections, and mortality from any cause during the study period</p>	<p>malignancies reduces invasive fungal infections, invasive yeast infections, invasive Aspergillus infections, and mortality. Bioavailability and dosing are significant factors because benefits are only derived from the oral or IV cyclodextrin solution and not the capsules. Therefore, the capsules are not recommended and the dosing should be at least 400 mg per day of the oral cyclodextrin solution or 200 mg per day of the IV solution.</p>
<p>Gotzsche & Johansen, 2004</p>	<p>Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (through November 2007)), and proceedings from the Interscience Conference on Antimicrobial Agents and Chemotherapy (1990–2007), General Meeting of the American Society of Microbiology (1990–2007), and European Congress of Clinical Microbiology and Infectious Diseases (1995–2007); the reference lists of articles were searched, and researchers in the field were contacted.</p> <p>Sample: 32 RCTs involving 4,287 patients with cancer who were neutropenic because of chemotherapy or HSCT; studies concerned with treatment or prevention of oral candidiasis were excluded. Most patients had acute leukemia or were undergoing HSCT.</p> <p>Treatment evaluated: prophylactic or empiric antifungal therapy (amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole) compared with placebo or no treatment in neutropenic patients with cancer</p> <p>Outcomes measured: mortality, fungal infection-related mortality, invasive fungal infection, colonization, use of additional antifungal therapy, harms</p>	<ul style="list-style-type: none"> • Prophylactic or empiric treatment with amphotericin B significantly decreased total mortality by 31%. • Prophylactic or empiric treatment with fluconazole, ketoconazole, miconazole, or itraconazole was not associated with a reduction in mortality. No eligible trials were found with voriconazole. • Amphotericin B and fluconazole significantly decreased mortality from fungal infection, by 55% and 58%, respectively. • Amphotericin B, fluconazole, and itraconazole significantly decreased the incidence of invasive fungal infection (by 59%, 61%, and 47%, respectively), but miconazole and ketoconazole did not. No eligible trials were found with voriconazole. • Prophylactic treatment with amphotericin B, fluconazole and ketoconazole significantly decreased fungal colonization. • The use of rescue antifungals was more common in the untreated group. • The reporting of adverse effects was too variable among the trials included to draw any meaningful conclusion. <p>Intravenous amphotericin B was the only antifungal agent that reduced total mortality. This may be the most relevant outcome measure since the drugs used may have adverse drug-related effects on mortality. For example, there are reports that azoles may increase the incidence of bacteremia. The authors concluded that intravenous amphotericin B should therefore be preferred for prophylactic or empirical antifungal therapy in neutropenic cancer patients.</p>
<p>Johansen & Gotzsche, 2000</p>	<p>Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (through November 2007)), and proceedings from the Interscience Conference on Antimicrobial Agents and Chemotherapy (1990–2007), General Meeting of the American Society of Microbiology (1990–2007), and European Congress of Clinical Microbiology and Infectious Diseases (1995–2007); the reference lists of articles were searched, and researchers in the field were contacted.</p> <p>Sample: 12 randomized trials with 1,895 neutropenic patients with cancer; most patients had acute leukemia or were undergoing HSCT.</p> <p>Treatment evaluated: lipid-soluble formulations of amphotericin B compared with conventional amphotericin B</p>	<ul style="list-style-type: none"> ▪ Lipid-based amphotericin B was not more effective than conventional amphotericin B for mortality. ▪ Lipid-based amphotericin B decreased invasive fungal infections by 35%. ▪ Lipid-based amphotericin B decreased nephrotoxicity by 55%. ▪ Lipid-based amphotericin B decreased dropouts from the study by 22%. <p>There was no significant difference in mortality for the drug used in most patients, AmBisome (3 trials, 1149 patients), whereas it tended to be more effective than conventional amphotericin B for invasive fungal infection (RR 0.63, 0.39 to 1.01, P = 0.053).</p> <p>Despite a significant reduction in invasive fungal infections and nephrotoxicity seen with lipid-based amphotericin B formulations, the authors concluded that an advantage was unclear regarding the use</p>

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Review Author	Study Information	Conclusions and Implications
	<p>Outcomes measured: mortality, invasive fungal infection, nephrotoxicity, serum creatinine, and dropouts</p>	<p>of lipid-based amphotericin B formulations if conventional amphotericin B is administered under optimal circumstances. In the trials reviewed, amphotericin B rarely was administered under optimal circumstances (routine premedication for the prevention of infusion-related toxicity and supplementation with fluid, potassium, and magnesium for the prevention of nephrotoxicity).</p>
<p>Johansen & Gotzsche, 2000</p>	<p>Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed (through November 2007), the proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) from 1990 to 2007, General Meeting of the American Society for Microbiology (ASM) from 1990 to 2007, and the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) from 1995 to 2007, and contacted researchers in the field, industry, and reviewed reference lists to identify unpublished trials.</p> <p>Sample: 17 RCTs with 3,798 neutropenic patients with cancer; most patients had acute leukemia or were undergoing HSCT.</p> <p>Treatment evaluated: fluconazole (oral or intravenous) compared with amphotericin B (oral or intravenous) in neutropenic patients with cancer; the antifungal agent was given prophylactically in 10 trials.</p> <p>Outcomes measured: mortality, invasive fungal infection, colonization, use of additional (escape) antifungal therapy, and adverse effects leading to discontinuation of therapy</p>	<p>No significant difference was found between fluconazole and amphotericin B with regard to</p> <ul style="list-style-type: none"> ▪ Mortality ▪ Invasive fungal infection ▪ Colonization ▪ Use of rescue therapy ▪ Dropouts. <p>The major adverse effects were hepatic impairment and gastrointestinal adverse effects with fluconazole and infusion-related toxicity, renal impairment and gastrointestinal adverse effects with amphotericin B.</p> <p>The authors noted that considerable heterogeneity existed in the studies and that amphotericin B was not favored in several of the largest trials through the trial design or data analysis. Of particular concern is that seven trials compared oral fluconazole to oral amphotericin B. Oral amphotericin B is poorly absorbed and is not recommended for prophylaxis or treatment of systemic fungal infections. None of the trial reports offered a rationale for this design and attempts by the authors of this meta-analysis to obtain additional information from the investigators were unsuccessful.</p> <p>In the ten trials that compared oral or intravenous fluconazole to intravenous amphotericin B, the design disfavored the amphotericin B arm. Clinicians familiar with the optimal administration of amphotericin B routinely prescribe premedication to prevent infusion-related toxicity and fluids, potassium and magnesium to prevent nephrotoxicity. Supplemental fluids, potassium and magnesium were not prescribed in any of the trials reviewed and premedication was prescribed in only two trials.</p> <p>The authors note that the majority of these trials were sponsored by the company that manufactures fluconazole and the authors were unable to obtain additional information or access to certain trial data held by the company.</p> <p>The authors concluded that there was not sufficient data from the available trials to judge the effectiveness of fluconazole compared with amphotericin B. Amphotericin B should be preferred because it is the only antifungal for which evidence suggests an effect on mortality.</p>
<p>Kanda et al., 2000</p>	<p>Search strategy: MEDLINE, CancerLit, and the Pfizer company database were searched through April 1999 (no start date provided). The search was not restricted to the English language or published trials.</p> <p>Criteria: Eligible studies were prospective, randomized, and compared oral fluconazole with placebo, no treatment, or oral polyenes (nystatin, oral amphotericin B). Eligible studies used a neutropenia definition of < 1,000/mcl</p>	<p>Prophylactic fluconazole was not effective in</p> <ul style="list-style-type: none"> ▪ Reducing fungal-related death in non-BMT recipients, although it was effective in BMT recipients ▪ Reducing proven systemic fungal infections in non-BMT recipients, although it was effective in BMT recipients. <p>Prophylactic fluconazole was effective in</p>

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Review Author	Study Information	Conclusions and Implications
	<p>and did not use IV antifungals. Studies had to report incidence of fungal infection. Sixteen trials with a total of 3,734 patients were used. Some studies exclusively examined BMT recipients, others studied non-BMT recipients, and others evaluated a combined population. Data from the meta-analysis were reported on combined population, BMT recipients only, and non-BMT recipients only.</p> <p>Treatment evaluated: The meta-analysis evaluated the efficacy of fluconazole prophylaxis during chemotherapy-induced neutropenia.</p> <p>Outcomes measured: Development of fungal-related death, systemic and superficial fungal infections, use of empiric IV amphotericin B, and infections or colonization with fluconazole-resistant fungi</p>	<ul style="list-style-type: none"> ▪ Reducing superficial fungal infections in both non-BMT and BMT recipients ▪ Reducing the use of amphotericin B for persistent neutropenic fever in the BMT population; however, this could not be concluded for the non-BMT group. <p>Prophylactic fluconazole did not increase</p> <ul style="list-style-type: none"> ▪ Rates of proven systemic infection with resistant strains in the non-BMT or BMT populations. <p>Colonization of fluconazole-resistant fungi did</p> <ul style="list-style-type: none"> ▪ Increase with prophylactic treatment in BMT recipients; however, information about non-BMT recipients is inconclusive because of lack of power and paucity of data.
<p>(Kuderer, Dale, Crawford, & Lyman, 2007)</p>	<p>Search strategy: Electronic databases through December 2006: Medline, EMBASE, Cancerlit, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effect, and Conference Proceedings (American Society of Clinical Oncology and American Society of Hematology). In addition, references from included articles and relevant published reports were hand searched, and references from leaders in the field were solicited. The literature search had no language restrictions.</p> <p>Criteria: Eligible studies were those of adult cancer patients receiving conventional-dose chemotherapy for solid tumors or malignant lymphoma and randomly assigned to primary G-CSF prophylaxis versus a placebo or untreated control group. Studies in which control patients received secondary G-CSF prophylaxis after the first cycle with the same myeloid growth factor were permitted. Primary G-CSF prophylaxis refers to G-CSF administration in the first cycle of chemotherapy before the onset of neutropenia, whereas secondary G-CSF prophylaxis is defined as G-CSF prophylaxis started in the chemotherapy cycle after the first episode of febrile neutropenia (FN). Patients may have received prophylactic antibiotics as long as they were permitted equally in both study arms. G-CSF must have been administered continuously until neutrophil recovery. Previous studies and guidelines concluded that myeloid growth factors are less effective if administered on the same day as chemotherapy, delayed more than 4 days following chemotherapy, or delayed until the onset of neutropenia. Therefore, studies were eligible only if the initiation of G-CSF was 1 to 3 days after the completion of myelosuppressive chemotherapy in each cycle. Studies were excluded if they used granulocyte-macrophage colony</p>	<p>Febrile neutropenia (FN) The occurrence of FN was reported as an outcome in 15 trials with 3,182 patients.</p> <ul style="list-style-type: none"> • G-CSF reduced the risk of febrile neutropenia by 46%. • FN occurred one or more times in 39.5% of controls and 22.4% of G-CSF patients, resulting in a weighted summary RR of 0.54 (95% CI, 0.43 to 0.67; $P < .0001$). • Filgrastim (RR = 0.61; 95% CI, 0.53 to 0.72) and lenograstim (RR=0.62; 95% CI, 0.44 to 0.88) had similar efficacy. • The single pegfilgrastim study demonstrated significantly greater efficacy (RR=0.08; 95% CI, 0.03 to 0.18) compared with filgrastim and lenograstim ($P < .0001$). <p>Infection-related mortality Infection-related mortality was reported as an outcome in 12 trials including 1,454 control patients and 1,463 patients receiving G-CSF.</p> <ul style="list-style-type: none"> • Overall, infection-related mortality was observed in 2.8% of controls and 1.5% of G-CSF patients, for a weighted summary RR of 0.55 (95% CI, 0.34 to 0.90; $P = .018$). • Reductions in infection-related mortality with G-CSF were observed among studies of filgrastim (RR=0.53; 95% CI, 0.30 to 0.92; $P = .024$). Statistical analysis of the subset of patients who received lenograstim or pegfilgrastim was not possible because the sample size was too low to detect differences. <p>Early mortality Early mortality was reported in 13 trials with 3,122 patients.</p> <ul style="list-style-type: none"> • Overall, early mortality was observed in 5.7% of control patients and 3.4% of G-CSF patients, resulting in a weighted summary RR of 0.60 (95% CI, 0.43 to 0.83; $P = .002$). • Reductions in early mortality with G-CSF were observed among studies of filgrastim (RR =0.60; 95% CI, 0.41 to 0.89; $P = .010$) and pegfilgrastim (RR =0.36; 95% CI, 0.13 to 0.99; $P = .047$) but not lenograstim (RR=0.84; 95% CI, 0.38 to 1.83; $P = .657$).

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	<p>stimulating factor, were studies of children or leukemia or multiple myeloma patients, included bone marrow or peripheral-blood stem-cell transplantation, or represented an economic analysis. Studies were also excluded if G-CSF was administered for established neutropenia or FN. Studies of patients receiving dose-dense or dose-escalation chemotherapy were excluded, as were studies that allowed differing drugs, doses, or schedules of chemotherapy or G-CSF in the different study arms.</p> <p>Sample: 17 RCTs of primary prophylactic G-CSF including a total of 3,493 patients. Ten studies (59%) used filgrastim, six (35%) used lenograstim, and one (6%) used pegfilgrastim.</p> <p>The cancer types consisted of solid tumors in 11 trials (65%) and aggressive non-Hodgkin's lymphoma in six RCTs (35%).</p> <p>Four RCTs (24%) were limited to elderly lymphoma patients. Eight studies used placebo control.</p> <p>At least three trials permitted secondary prophylaxis with G-CSF in control patients, with only two reports explicitly prohibiting this use of G-CSF. Eleven trials failed to specify whether secondary prophylaxis with G-CSF was allowed in controls.</p> <p>Prophylactic antibiotics were used in three trials, prohibited in five trials, and not specified in eight trials.</p> <p>Treatment evaluated: Primary G-CSF prophylaxis versus a placebo or untreated control group</p> <p>Outcomes measured: Primary outcome: proportion of patients with FN. Secondary outcomes: infection-related mortality, all early mortality (all-cause mortality during chemotherapy period), relative dose-intensity (RDI), and bone pain or musculoskeletal pain.</p>	<p>Relative dose intensity (RDI) RDI was reported as an outcome in 10 trials. The average RDI among control patients in these studies ranged from 71.0% to 95.0%, with a mean RDI of 86.7% (median RDI, 88.5%).</p> <ul style="list-style-type: none"> Among G-CSF-treated patients, the average RDI ranged from 91.0% to 99.0%, with a mean RDI of 95.1% (median RDI, 95.5%). RDI differences between study arms ranged from 2.8% to 20.0%, with average differences of 8.4% ($P = .001$). None of the 10 G-CSF treatment arms reported an average RDI of less than 90%, whereas six of 10 control groups reported a mean RDI of less than 90%, with four control arms averaging an RDI of $\leq 85\%$. <p>Bone and Musculoskeletal Pain Bone or musculoskeletal pain during the course of chemotherapy was reported as an outcome in 14 trials including 3,029 patients.</p> <ul style="list-style-type: none"> Bone pain was reported in 10.4% of controls and 19.6% of G-CSF-treated patients, for a weighted summary RR of 4.023 (95% CI, 2.156 to 7.52; $P < .0001$).
<p>Lyman et al., 2003</p>	<p>Search strategy: The search strategy and time period were not described.</p> <p>Criteria: Trials were not all RCTs; in fact, very little background given for the discussed studies.</p> <p>Treatment evaluated: The systematic review evaluated age and risk of neutropenia and its complications (primarily febrile neutropenia and severe neutropenia). It summarized evidence on clinical, economic, and quality-of-life effects on older patients receiving chemotherapy.</p>	<p>Older individuals receiving myelosuppressive chemotherapy are at increased risk for severe and febrile neutropenia.</p> <p>One study of non-Hodgkin lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy found that the risk of developing febrile neutropenia during the first cycle was doubled in patients \geq age 65 as compared with patients younger than age 65.</p> <p>Older patients with febrile neutropenia have greater mortality rates and a greater risk of serious medical complications than their younger counterparts.</p> <p>A systematic review of older non-Hodgkin patients with lymphoma showed that the use of G-CSF is associated with a decreased risk of severe and febrile neutropenia.</p>

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	<p>Outcomes measured: Primarily febrile neutropenia and severe neutropenia.</p>	<p>The use of G-CSF is associated with cost savings when used in high-risk patients (e.g., older adults) who have a $\geq 20\%$ risk of developing febrile neutropenia.</p> <p>Studies support primary prophylaxis with G-CSF in patients aged ≥ 70 who are being treated with CHOP or chemotherapy of similar intensity.</p> <p>Studies support the subsequent use of G-CSF in older patients who experience severe febrile neutropenia and anemia during cycle 1 of adjuvant chemotherapy for early-stage breast cancer.</p> <p>Note: Results often did not include a breakdown of older and younger patients' results.</p> <p>The definition of "older" varied (i.e., 60+, 65+, or 70+)</p>
<p>Lyman et al., 2002</p>	<p>Search strategy: MEDLINE, EMBASE, Cochrane Library, and hand searches of references from published reports</p> <p>Sample: 8 RCTs, including 1,144 patients receiving chemotherapy for solid tumors (n=753) or malignant lymphomas (n=391); studies of patients who were receiving high-dose therapy that required stem cell or BMT support or who were being treated for acute or chronic leukemia were excluded.</p> <p>Treatment evaluated: CSFs administered prophylactically, before the onset of neutropenia or fever, compared with concurrent placebo or untreated controls not allowing any dose escalation</p> <p>Outcomes measured: febrile neutropenia, documented infection, infection-related mortality, patient reports of bone pain, and reduction in the dose of chemotherapy or delay in chemotherapy treatment</p>	<p>The overall mean risk of febrile neutropenia was 51% among patients NOT receiving CSFs and the overall mean risk of febrile neutropenia was 32% among patients receiving CSFs.</p> <p>CSFs significantly reduced</p> <ul style="list-style-type: none"> ▪ Febrile neutropenia by 37% ▪ Documented infections by 6% ▪ Chemotherapy dose reduction or treatment delay by 20%. <p>CSFs increased the risk of</p> <ul style="list-style-type: none"> ▪ Bone pain by 15%. <p>CSFs did not improve infection-related mortality.</p> <p>The authors concluded that CSFs are effective in reducing the risk of febrile neutropenia, documented infections, and chemotherapy dose reductions or delays, but they increase the risk of bone pain. CSFs had no impact on infection-related mortality.</p>
<p>Ring et al., 2002</p>	<p>Search strategy: PubMed 1992–2002, using influenza, vaccination, immunization, cancer, and malignancy as search terms; no restrictions were placed on the language of the publications. Additional data were acquired by direct communication with vaccine manufacturers.</p> <p>Sample: 11 studies measuring seroconversion after influenza vaccination; no comments existed regarding the research design of the studies, but five studies included a control group.</p> <p>Treatment evaluated: influenza vaccination in patients with cancer</p> <p>Outcomes measured: seroconversion after influenza vaccination; protective antibody titres are defined as reciprocal serum titres greater than or equal to 40 (= 1/40), or a fourfold increase in titres from before vaccination.</p>	<p>Seroconversion rates following influenza vaccination ranged from 10%–78% in patients with cancer as compared with 56%–94% in healthy controls.</p> <p>Seroconversion rates following influenza vaccination ranged from 37%–52% in patients with cancer on chemotherapy as compared with 76%–92% of patients with cancer not receiving chemotherapy.</p> <p>One study of 42 adult patients with hematologic or oncologic disorders found that the seroconversion rate following influenza vaccination was 50% if the vaccine was given at the time of chemotherapy compared with 93% if the vaccine was given between cycles.</p> <p>The studies found in the literature search were characterized by small sample sizes and an absence of stratification for tumor type, stage, chemotherapy schedule, vaccination type, or immune function. Nonetheless, the studies demonstrate that</p> <ul style="list-style-type: none"> • Serologic responses to different viral antigens may vary considerably within individual patients.

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Review Author	Study Information	Conclusions and Implications
		<ul style="list-style-type: none"> • Responses to vaccination often are inferior to those seen in historic healthy controls. • Immunocompromise resulting from tumor type (hematologic malignancy versus solid tumors) or treatment (standard chemotherapy versus stem cell transplantation) may correlate with efficacy of the vaccination. Patients with hematologic malignancies or stem cell transplant recipients may have an inferior response to vaccination. • The timing of vaccination with respect to chemotherapy may be critical.
Sung et al., 2004	<p>Search strategy: OVID MEDLINE (1966–July 2003) and EMBASE (1980–July 2003); the search was limited to RCTs that included children ≤ 18 years old. References were hand searched for relevant literature, and conference proceedings from meetings of the American Society of Hematology, American Society of Clinical Oncology, Society Internationale Oncologie Pediatric, and the American Society of Pediatric Hematology/Oncology from January 2001–January 2003 were reviewed. Manufacturers of G-CSF and GM-CSF were contacted.</p> <p>Sample: 16 RCTs, including 1,183 children, 592 of whom were randomized to CSF and 591 to the control arm; five studies evaluated GM-CSF, and 11 examined G-CSF.</p> <p>Treatment evaluated: CSFs given to children with cancer prophylactically after initiation of chemotherapy prior to the development of febrile neutropenia</p> <p>Outcomes measured: febrile neutropenia, duration of neutropenia, duration of hospitalization, rate of documented infection, duration of parenteral antibiotics, rate of amphotericin use, duration of chemotherapy delay, and infection-related mortality</p>	<p>In children with cancer</p> <ul style="list-style-type: none"> • CSFs reduced the rate of febrile neutropenia by 20%. • CSFs reduced hospitalization duration by two days. • CSFs reduced the documented infection rate by 22%. • CSFs reduced the duration of neutropenia by four days. • CSFs reduced the rate of amphotericin use by 50%. • CSFs were not associated with a reduction in infection-related mortality. • CSFs were not associated with a difference in duration of parenteral antibiotics. • CSFs were not associated with a difference in the duration of chemotherapy delay. <p>The rates of febrile neutropenia in all of the included studies were ≥ 39%, so the researchers concluded that prophylactic CSFs should be used in children with cancer who are receiving chemotherapy with an anticipated rate of febrile neutropenia ≥ 40%. No explicit measurement of quality of life exists, but researchers hypothesize that decreasing hospitalization and febrile neutropenia would contribute to improved quality of life.</p>
Sung et al., 2007	<p>Search strategy: The standard Quality of Reporting of Meta-Analyses (QUOROM) guidelines were used to guide the search. Electronic searches of Ovid MEDLINE from 1966 to April 24, 2007, EMBASE from 1980 to April 26, 2007, and of the Cochrane Central Register of Controlled Trials Register (CENTRAL) through the second quarter of 2006 were performed. The pharmaceutical manufacturers of G-CSFs and GM-CSFs were also contacted.</p> <p>Sample: 148 RCTs including 16, 839 participants or cycles; 8474 were randomly assigned to CSF and 8365 to placebo or no treatment. The RCTs included adult and/or pediatric patients with cancer undergoing chemotherapy or HSCT. The results were analyzed at the study level, not at the patient level.</p> <p>Criteria:</p> <ol style="list-style-type: none"> 1) Patients were randomly assigned to CSFs or to placebo or no therapy 2) CSFs were given concurrently with or after initiation of chemotherapy or 	<p>Compared with control, prophylactic CSFs did not significantly affect:</p> <ul style="list-style-type: none"> • Overall all-cause mortality (7.6 % rate in CSF group and 8.0% in control group) • Risk for infection-related mortality (3.1% rate in CSF group and 3.8% in control group) <p>Compared with control, prophylactic CSFs significantly reduced:</p> <ul style="list-style-type: none"> • Documented infections by 15% • Microbiologically documented infections by 14% • Clinically documented infections by 25% • Episodes of febrile neutropenia by 29% • Duration of febrile neutropenia by a mean difference of 1.38 days • Duration of fever by a mean difference of 0.45 days • Time to ANC ≥ 500 cells/mcL by a mean difference of 3.79 days • Time to ANC ≥ 1000 cells/mcL by a mean difference of 5.03 days • Duration of parenteral antibiotic therapy by a mean difference of 1.81 days • Duration of hospitalization by a mean difference of 2.41 days

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Review Author	Study Information	Conclusions and Implications
	<p>conditioning for SCT but before neutropenia developed</p> <p>3) Chemotherapy or conditioning regimens or other supportive care was not planned to systematically differ between study groups.</p> <p>Treatment evaluated: Prophylactic CSFs given concurrently with or after initiation of chemotherapy prior to the development of neutropenia compared with placebo or no therapy in patients with cancer undergoing chemotherapy or HSCT.</p> <p>Outcomes measured: The primary outcome measure was short-term all-cause mortality. Secondary outcomes included infection- related mortality, documented infections, microbiologically documented infections, clinically documented infections, episodes and duration of febrile neutropenia, duration of fever, duration of neutropenia, duration of parenteral antibiotic therapy, and duration of hospitalization.</p>	<p>Other observations: The median rate of febrile neutropenia in the placebo groups was 44.2% vs. 25.3% in the CSF groups. The use of G-CSFs had a greater effect than use of GM-CSFs on reducing documented infections and febrile neutropenia, but all-cause mortality and infection-related mortality did not differ.</p>
van de Wetering et al., 2005	<p>Search strategy: MEDLINE from 1966–October 2002, EMBASE from 1988–October 2002, and the Cochrane Central Register of Controlled Trials, issue 2, 2002; the references were checked for additional articles. Authors of included papers were contacted.</p> <p>Sample: 22 randomized trials of patients with cancer undergoing chemotherapy</p> <p>Treatment evaluated: Randomized trials that compared oral-based prophylactic antibiotics with placebo or no prophylaxis were compared quinolone-based prophylaxis to trimethoprim-sulfamethoxazole–based regimens. Trials considering patients with cancer (both adults and children) undergoing chemotherapy where oral prophylactic antibiotics were started before the expected onset of neutropenia were included.</p> <p>Outcomes measured: documented bacteremia, infection-related mortality, fungemia, and fungal-related mortality</p>	<p>Antibacterial prophylaxis (trimethoprim-sulfamethoxazole or quinolones) significantly reduced</p> <ul style="list-style-type: none"> ▪ Bacteremia by 57% ▪ Infection-related mortality. <p>Quinolones significantly reduced the risk of gram-negative bacteremia, but trimethoprim-sulfamethoxazole did not</p> <ul style="list-style-type: none"> • Significantly reduced the risk of gram-positive bacteremia, but quinolones did not. <p>No significant increase was reported in the risk of fungemia or fungal-related mortality with antibacterial prophylaxis.</p> <p>In subgroup analyses, a significant reduction was found in bacteremia in patients undergoing conventional chemotherapy and BMT.</p>
Meta-analyses and Reviews of Studies Related to Prevention of Infection for Neutropenic Patients With Cancer		
PEP Weight of Evidence Category: Recommended for Practice		
Larson & Nirenberg, 2004	<p>Search strategy: PubMed, CINAHL, and National Guideline Clearinghouse, 1980–June 2003. The Cochrane Database of Systematic Reviews was reviewed for clean food and water, protective environment and clothing, skin care, and oral hygiene. Studies related to BMT were excluded (rationale provided).</p> <p>Sample: Literature review</p>	<ul style="list-style-type: none"> • Ice chips to prevent mucositis: PRISM evidence rating: I-1 • Influenza immunization for staff: PRISM evidence rating: I-3 • Low microbial diet: PRISM evidence rating: II- 4 • High-efficiency masks worn outside patient rooms, private room isolation, and oral regimens to prevent mucositis: PRISM evidence rating: II-6 • Protective isolation (no gowns and antiseptic bathing, visitors and pets restricted, flowers and plants restricted): PRISM evidence rating: III-7

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Review Author	Study Information	Conclusions and Implications			
	<p>Criteria: PRISM level of evidence was used to rate interventions.</p>	<p>A low level of evidence exists for most aspects of managing hospitalized neutropenic patients. Most interventions are based on tradition and theoretical considerations rather than evidence. Larger sample sizes and stratification by disease type and severity are required.</p> <p>More collaboration is needed among clinicians and researchers to identify and systemically evaluate nursing interventions to improve care.</p>			
Wilson, 2002	<p>Search strategy: A 25-year literature search of OVID and MEDLINE databases was conducted. Search terms included neutropenia, diet, nursing care, precautions, isolation, and patient care. Studies with only pediatrics, BMT, or stem cell transplant were excluded. Additionally, Web sites for the Centers for Disease Control and Prevention, Occupational Safety and Health Administration, and other agency or institutional policies related to infection control were searched.</p> <p>Sample: No pediatric studies were included.</p> <p>Criteria: No explicit criteria were described.</p>	<p>The following recommendations were adopted based on synthesis of the evidence.</p> <ul style="list-style-type: none"> • Hand washing • All fruits and vegetables washed carefully with tap water prior to ingestion • Unwashed or raw meat, eggs, fish, and shellfish should be excluded from the diet. 			
Moody et al., 2002	<p>Search strategy: Not described; key words were bacterial translocation, low bacterial diet, neutropenia, and protected environment.</p> <p>Sample: 7 studies</p> <p>Outcomes measured: Percent of days with neutropenia, clinical infection, and percent of stool cultures with no growth</p>	<p>A paucity of research and lack of evidence do not support a neutropenic diet; however, it has remained the standard of practice for more than 20 years.</p> <p>Table summarizes clinical trials of total protected environments. Combined, the studies suggest that protected environments may offer some protection from infection independent of antibiotics. The role of a neutropenic diet is unclear, and no evidence supports a role in preventing infections.</p> <p>Smith and Besser (2000) surveyed 400 hospitals of association of community cancer centers: 152 hospitals responded, 78% use some form of neutropenic diet for patients with ANC < 1,000, and 70% advised outpatients to follow the diet at home. High variability existed concerning the pattern of use and content of the diet.</p>			
Somerville, 1986	<p>Search strategy: Not described.</p> <p>Sample: Literature review of special diets for neutropenic patients</p> <p>Study question: Does the oral ingestion of food potentially contaminated with pathogenic organisms increase infections in neutropenic patients with cancer?</p>	<p>Another study concluded that evidence was inadequate to suggest a benefit of a special diet regardless of isolation type used.</p> <p>One study suggested that eating salad was a potential risk.</p> <p>No documented studies determined whether ingestion of potentially pathogenic organism actually causes infection.</p> <p>Recommended: Avoid eating fresh fruits or vegetables, drink sterile water, avoid drinking canned beverages, avoid processed meats, and wash lids of canned food and beverages.</p>			
Shelton, 2003	<p>Search strategy: Specifics and criteria for inclusion were not discussed. The literature was reviewed for best practice in management of neutropenia in patients with cancer (e.g., environmental manipulations, prophylaxis against infection, patient care practices, evaluation and treatment of neutropenic fever).</p>	Interventions	ONS Evidence Rating (by original author)	PRISM Evidence Rating (by current authors)	
<ul style="list-style-type: none"> • Environmental manipulations • High-efficiency particulate air filtration for patients 			Moderate	II-7	

Prevention of Infection
Systematic Reviews / Meta-analysis Table

Review Author	Study Information	Conclusions and Implications		
	<p>Sample: research studies, review articles, and book chapters</p> <p>Criteria: Oncology Nursing Society evidence-based practice rating was used.</p> <ul style="list-style-type: none"> • Strong evidence: multiple randomized, controlled studies in various patient populations • Moderate evidence: a few studies in comparable patient populations, with some design bias or sampling limitations • Some evidence: limited support through clinical studies, sound scientific theory basis for practice • Weak evidence: lack of scientific support for a practice or strong studies refuting benefit of this practice 	<p>receiving stem cell transplantation</p> <ul style="list-style-type: none"> • No fresh flowers or plants 	<p>High</p>	<p>II-7</p>
		<p>Prophylaxis against infection</p> <ul style="list-style-type: none"> • Antimicrobial • Primary prophylaxis with CSF associated with consolidation chemotherapy • Use of high particulate filter mask when outside high-efficiency particulate air filtered room 	<p>High Moderate Weak</p>	<p>II-7 II-7 II-7</p>
		<p>Patient care practices</p> <ul style="list-style-type: none"> • Good hand hygiene • No routine barrier precautions and protective isolation • No special dietary limitations • Frequent oral care • Rinse mouth with antimicrobial mouth rinses when poor oral hygiene or gingivitis is present. • Permanent central venous catheter is not placed when patient is neutropenic. 	<p>High Moderate Moderate High High High</p>	<p>II-7 II-7 II-7 II-7 II-7 II-7</p>
		<p>Primarily based on patients with leukemia. Conclusions may be extrapolated to other patients with prolonged neutropenia.</p>		

Prevention of Infection
Systematic Reviews / Meta-analysis Table

Review Author	Study Information	Conclusions and Implications
Smith & Kagan, 2005	<p>Search strategy: Specifics were not described. Literature from 1980 was searched.</p> <p>Sample: published articles, books, and brochures; 24 studies that were mostly hospital based, with 3–5 pertaining to community or home environment</p> <p>Generally were environmental surveillance and retrospective cohort studies</p> <p>Criteria: not provided</p>	<p>Factors associated with invasive fungal infections:</p> <ul style="list-style-type: none"> • Chemotherapy or radiotherapy • Long-term broad-spectrum antibiotic use • Neutropenia: greatest risk ANC < 500 and more than 12–15 days • Fungal colonization • Allogeneic HCT • Steroid use for treatment of graft-versus-host disease • Prior fungal infection • IV catheters • Environmental contamination <p>Recommendations for decreasing fungal pathogens (see Table 4 in the article)</p> <p>Recommendations to reduce exposure of fungal pathogens at home (see Table 5 in the article)</p> <p>Recommendations to reduce exposure to fungal pathogens through dietary measures (see Table 7 in the article)</p>