ONS Putting Evidence into Practice

Prevention of Infection

Evidence Table

(Literature search completed through May 2008)

Author and Year	Characteristics of the Intervention	Sample Characteristics, Setting Characteristics, Study Design, and Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions and/or Contraindications, Special Training Needs, and Costs
Antibacterial prophylaxis with quinolones for patients at high risk for infection					
PEP Weight of Evidence Category: Recommended for Practice					
Bucaneve et al., 2005	Adult patients with cancer whose chemotherapy-induced neutropenia (absolute neutrophil count [ANC] < 1,000) was expected to occur for more than seven days were treated with oral levofloxacin 500 mg or placebo from the start of chemotherapy until the resolution of neutropenia.	N = 760 Hospitalized adult patients with cancer who were expected to develop chemotherapy-induced neutropenia lasting longer than seven days; the sample included patients with the following types of cancer: 49% leukemia, 31% non-Hodgkin lymphoma or Hodgkin disease, 13% other hematologic cancers, and 7% solid tumors. 35 medical centers in Italy, inpatient setting Prospective, multicenter, randomized, double- blind, placebo-controlled trial No conceptual model was described. Primary endpoint: Incidence of fever Secondary endpoints: Type and number of microbiologically	Patients were examined daily for signs of infection. In the event of fever or suspected infection, microbiologic cultures were obtained, including at least 2 separate blood cultures. Parenteral antimicrobials were initiated according to clinical judgment. Standard methods were used to determine identification and susceptibility of microbiologic cultures. Infections were classified according to definitions of the European Organization for Research and Treatment of cancer (EORTC). Compliance was determined by counting pills.	The incidence of fever (axillary temperature 38.5°C or higher, or 38°C at least twice during a 12-hour period) was 65% in the levofloxacin prophylaxis group versus 85% in the placebo group ($p = 0.001$). Microbiologically documented infection occurred in 22% of patients in the levofloxacin group and 39% of patients in the control group (absolute risk reduction 17%, 95% confidence interval [CI] 24 to 10%, $p < 0.001$). In the levofloxacin group, the incidence of bacteremias (risk reduction 16%, 95% CI 22 to 9%, $p < 0.001$) and single-agent gram-negative bacteremias (risk reduction of 7%, 95% CI 10 to 2%, $p < 0.01$) was lower. Death from infection occurred in 2.4% of patients in levofloxacin group and 3.8% of patients in control	Populations with a low risk of neutropenia were not included. Most of the patients had hematologic malignancies, so the study supports the use of antibacterial prophylaxis in this population. The study cannot be generalized to patients who have solid tumors or who are neutropenic for less than seven days. Survival advantage with antibiotic prophylaxis was not demonstrated in the study. There is concern that routine use of antibiotics is associated with an increase in resistant organisms. Discussion states that the study provides evidence that prophylaxis is economical because risk of fever is reduced.

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		documented infections Use of parenteral antimicrobials Compliance Tolerability Survival		group (p = 0.36) (Sample size was inadequate to determine the effect on death rate from infection). The median duration of prophylaxis was 14 days for patients with solid tumors or lymphoma and 25 days for patients with leukemia. The median duration of neutropenia (ANC < 1,000) was 8 days in patients with solid tumors or lymphoma and 15–19 days in patients with leukemia. Overall mortality was 3% in the levofloxacin group and 5% in the placebo group (p = 0.15). Infection-related mortality was 2% in the levofloxacin group and 4% in the placebo group (p = 0.36). Compliance and reported adverse events were similar in both groups. In the levofloxacin group, three patients reported gastrointestinal disturbances, three patients	The total cost of antibiotics per patient was less in the levofloxacin treated group. The mean cost of antibiotics was €1,953 in the levofloxacin group and €2,841 in the control group.

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				reported rash, and one reported seizure. In the control group, two patients reported rash and one reported rhabdomyolysis. The prevalence of fluoroquinolone-resistant bacteremias was 41 of 339 (12%) in the levofloxacin group and 32 of 336 (9.5%) in the control group, but this result was not statistically significant. However, the bacteremias that developed in the levofloxacin group were more likely to be resistant to levofloxacin than the bacteremias that developed in the control group. The incidence of levofloxacin-resistant bacteremias was 41 of 47 (87%) bacteremias in the levofloxacin group and 32 of 68 (47%) bacteremias in the control group.	
Cullen et al., 2005	Adult patients with cancer receiving cyclic chemotherapy for solid tumors or lymphoma who were at risk for temporary, severe neutropenia (ANC < 500/mm^3) were treated with	N = 1,565 Adults starting chemotherapy for solid tumors or lymphomas; eligible regimens were known to be associated with a risk of neutropenia	The measures used to determine fever were not specified in the paper. If infection was suspected, patients were evaluated and treated according to	The incidence of fever (> 38°C) attributed to infection during the first cycle was 3.5% in the levofloxacin group versus 7.9% in the placebo group ($p < 0.001$).	Microbiologic evidence was not required for primary outcome. Some febrile episodes may have been related to causes other than bacterial

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	oral levofloxacin 500 mg or matching placebo daily for seven days during the expected neutropenic period. Treatment began on day 5 for regimens associated with early onset of neutropenia (e.g., docetaxel), day 8 for 14-day and 21-day cycles, and day 15 for 28-day cycles. Patients were in the trial for as many as six cycles of treatment.	(ANC < 500/mm^3) but were not routinely given with granulocyte–colony-stimulating factor (G-CSF) support. The sample included patients with the following types of cancer: 35% of patients received FEC (cyclophosphamide, epirubicin, and 5-fluorouracil) or AC (adriamycin and cyclophosphamide) for breast cancer, 14% received BEP (bleomycin, etoposide, and cisplatin) or EP (etoposide and cisplatin) for testicular cancer, 14% received treatment for small cell lung cancer, 10% with non-Hodgkin lymphoma, 8% with non-small cell lung cancer, 3% with Hodgkin disease, 3% with ovarian cancer, 2.5% with gastric cancer, 2.5% with esophageal cancer, 2% with bladder cancer, 1% with sarcoma, and 1% with colorectal cancer. Exclusion: planned use of G-CSF	clinical findings and local policy. Compliance was assessed by patient report and pharmacists counting pills.	During the entire course, at least one fever occurred in 10.8% of the levofloxacin group versus 15.2% of the placebo group (p = 0.01). Rates of probable infection were 34.2% and 41.5% in the levofloxacin and placebo groups, respectively (p = 0.004). Hospitalization because of infection occurred in 15.7% of the levofloxacin group and 21.6% of the placebo group (p = 0.004). Rates of severe infection were underpowered, and respective rates were 1% and 2% (p = 0.15). The median ANC at onset of infection was 300 in patients in the levofloxacin group and 520 in patients in the control group. The incidence of mucosal candidiasis was 4.7% in patients in the levofloxacin group and 5.1% in patients in the control group,	infection (e.g., viral infection). Mortality data were not collected. Antibiotic resistance data were not obtained but are a concern in repeated prophylaxis. Subjectivity of the secondary outcome of “probable infection” was dependent on physician judgment.

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		60 oncology centers in the United Kingdom took part in the study. Prospective, multicenter, randomized, double- blind, placebo-controlled trial No conceptual model was described. Primary endpoint: Incidence of clinically documented febrile episodes, defined by core body temperature > 38°C attributed to infection. Secondary endpoints: Incidence of probable infections defined by at least one of the following: Clinically documented febrile episode; other signs of systemic response to infection, such as hypothermia (temperature < 35.6°C), low grade fever (temperature 37.5-37.9°C), tachycardia (> 90 beats per minute), or tachypnea (> 20 breaths per minute); signs of a focus of infection; or the use of antibacterial		suggesting that antibiotic prophylaxis did not cause an increase in fungal infections. 40%–45% of fevers and probable infections occurred outside of the expected nadir. Antibiotic susceptibility data were not recorded completely, so the incidence of fluoroquinolone-resistant infections is unknown.	

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		therapy. Incidence of hospitalization for infection. Frequency of severe infection, defined by the presence of infection-related sepsis syndrome or death from infection. Site of infection. ANC at onset of infection.			
Cullen, Billingham, Gaunt, Steven, 2007	Adult patients with cancer receiving cyclic chemotherapy for solid tumors or lymphoma who were at risk for temporary, severe neutropenia (ANC < 500/mm^3) were treated with oral levofloxacin 500 mg or matching placebo daily for seven days during the expected neutropenic period. Treatment began on day 5 for regimens associated with early onset of neutropenia (e.g., docetaxel), day 8 for 14-day and 21-day cycles, and day 15 for 28-day cycles. Patients were on study for a mean of 4.4 cycles of chemotherapy, with 45% of patients completing	N = 1,565 Adults starting chemotherapy for solid tumors or lymphomas; eligible regimens were known to be associated with a risk of neutropenia (ANC < 500/mm^3) but were not routinely given with granulocyte–colony-stimulating factor (G-CSF) support. The sample included patients with the following types of cancer: 35% of patients received FEC (cyclophosphamide, epirubicin, and 5-fluorouracil) or AC (adriamycin and cyclophosphamide) for breast cancer; 14% received BEP (bleomycin, etoposide, and cisplatin) or	The primary outcome measure described in the original trial report (Cullen et al., 2005) was the incidence of clinically documented febrile episodes (FEs), defined as a core temperature exceeding 38°C, attributed to infection. The original results demonstrated a reduction in FEs in patients receiving levofloxacin. However, the use of prophylactic antibiotics may increase the rate of antibiotic resistance, so the data from the original study were analyzed to determine which patients benefit most from prophylactic antibiotics. The analysis measured rates of	An FE and HTSI during first versus later cycles of chemotherapy 119 of 784 (15.2%) controls had at least one FE during chemotherapy. Of the controls that had an FE, 62 of 119 (52%) controls had an FE during cycle 1. The per-cycle FE rate for the first cycle was 8.0% (62 of 772; data missing for 12 patients) compared with 3.3% (89 of 2687) in non–first cycles. Of the 784 control patients, 169, of whom 81 (48%) experienced HTSI during the first cycle, had HTSI at least once during chemotherapy; thus, the per-patient	Secondary analysis The primary outcome is the incidence of FEs rather than documented infections, and a reduction in documented infections may be a more meaningful endpoint. The sample is at low risk for febrile neutropenia. An important consideration for low-risk patients with short durations of neutropenia is whether quinolone prophylaxis is of greater benefit than the option of outpatient quinolone treatment for fever and neutropenia, should it occur. Both the National Comprehensive Cancer

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	six cycles.	EP (etoposide and cisplatin) for testicular cancer; 14% received treatment for small cell lung cancer, 10% with non-Hodgkin lymphoma, 8% with non-small cell lung cancer, 3% with Hodgkin disease, 3% with ovarian cancer, 2.5% with gastric cancer, 2.5% with esophageal cancer, 2% with bladder cancer, 1% with sarcoma, and 1% with colorectal cancer. Seven hundred eighty-four patients were randomly assigned to the placebo arm and received 3,459 cycles of chemotherapy (mean = 4.4 cycles per patient). Random assignment of patients in the SIGNIFICANT trial was stratified by age (< 40, 40–59, and ≥ 60 years) and cancer type (breast, testicular, small cell lung, Hodgkin disease, and Non -Hodgkin lymphoma [NHL], and	FE across all cycles, calculated as the proportion of randomly assigned patients experiencing the event at least once during the chemotherapy program (per patient FE rate). The analysis separates events in cycle 1 because chemotherapy dose reductions and possibly antibiotic resistance may affect later cycles. Per cycle FE rates are calculated as the proportion of observed cycles in which an event occurs. Rates of hospitalization for the treatment of suspected infection (HTSI) also were analyzed. HTSI occurred in a subset of patients with FEs and also in some patients not meeting the trial criteria for an FE.	hospitalization rate was 21.6%. The per-cycle HTSI rate during first and non-first cycles was 10.5% and 4.8%, respectively. The risk of both outcomes was much greater for the first cycle, and approximately 50% of episodes occurred in cycle 1. If no FE occurred in cycle 1, the rate of FE was 2.6% for cycle 2 and 2.5% per cycle for cycles 2 to 6. However, if an FE occurred in cycle 1, then the corresponding rates were much higher: 15.5% in cycle 2 and 12.6% per cycle in cycles 2 to 6. Treatment benefit of quinolone prophylaxis was present across all cycles. As reported by Cullen et al. (2005), the per-patient FE rate was 10.8% (84 of 781) for patients receiving levofloxacin compared with 15.2% for patients receiving placebo (119 of 784), giving a statistically significant reduction in the	Network and the Infectious Diseases Society of America recommend oral quinolone-based regimens as outpatient empirical therapy for neutropenic fever in adults meeting criteria for low risk for complications. Use of quinolone prophylaxis may preclude later use of the regimens as empirical therapy for neutropenic fever in the same patient. Guidelines on outpatient management of adults with neutropenic fever assume that quinolones were not used as prophylaxis and the use of quinolones for prophylaxis precludes their use for treatment. Another important consideration for low-risk patients is whether the potential benefit of antibacterial prophylaxis outweighs the risk of antibiotic resistance.

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		others). Exclusion: planned use of G-CSF 60 oncology centers in the United Kingdom took part in the study. Prospective, multicenter, randomized, double- blind, placebo-controlled trial with secondary univariate and multivariate analysis No conceptual model was described.		risk of FE (odds ratio = 0.67; 95% confidence interval = 0.50–0.91; p =0.009). For the first cycle only, the per-patient FE rate was 3.5% in patients receiving levofloxacin compared with 7.9% in controls (odds ratio = 0.42; 95% confidence interval = 0.26–0.66; p =0.0001), whereas for non–first cycles, the per-patient FE rate was 7.8% (61 of 781) and 9.8% (77 of 784), respectively (odds ratio = 0.78; 95% confidence interval = 0.55–1.11; p = 0.16). Per-cycle FE rates in cycle 2 and cycles 2 to 6 indicate that prophylactic benefit is gained in the small number of patients who experience an FE in cycle 1, but not in the much larger group of patients who do not experience an FE in cycle 1. If patients had an FE in cycle 1, 15.5% of controls had an FE in cycle 2 and 9.5% of patients receiving	

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				levofloxacin had an FE in cycle 2; compared with 2.6% and 3.1%, respectively, if no FE occurred in cycle 1. In summary, the data suggest that the benefit of antibiotics is greatest in those who experience an FE in cycle 1 because they are at higher risk of developing an FE in subsequent cycles compared with patients who do not develop an FE in cycle 1.	
Lalami et al, 2004	G-CSF (5 mcg/kg subcutaneous) or G-CSF with antibiotics (ciprofloxacin 500 mg by mouth every eight hours and amoxicillin 500 mg by mouth or clavulanate 125 mg by mouth every eight hours) daily starting 48 hours after chemotherapy and continuing until ANC is > 2,000 cells/ mm³. Patients were included in the study for one treatment cycle. Secondary prevention of febrile neutropenia with G-	N = 48 Eligible patients were adults who received chemotherapy for solid tumors and had experienced a prior episode of febrile neutropenia. Patients were scheduled to continue on the same regimen without dose reduction. Most patients were receiving treatment for breast, ovarian, or lung cancer. Two sites in Europe, setting	Patients were evaluated with regular complete blood counts (CBC), temperature monitoring once daily, and observation for adverse effects of the prophylactic antibiotics. In the event of a fever, the antibiotic prophylaxis was discontinued and a complete clinical evaluation for infection was completed.	No episodes of febrile neutropenia occurred in the G-CSF group, and only one incident of febrile neutropenia was reported in the combined group(p = 1). G-CSF reduced the risk of febrile neutropenia recurrence. Antibiotics did not provide any additional benefit in terms of prophylaxis. Reported side effects were similar and mild.	Not placebo controlled, not blinded Patients were not stratified, and the groups were not balanced, particularly by disease and the number of prior chemotherapy cycles. The study was inadequately powered, since the frequency of the outcome measure was close to none (febrile neutropenia episodes). Cost implications were

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	CSF and antibiotics	not described Prospective, randomized pilot trial No conceptual model was described.			discussed but not in detail.
Antifungal prophylaxis to prevent fungal infections in high-risk patients					
PEP Weight of Evidence Category: Recommended for Practice					
Cornely et al., 2007	Study patients received 200 mg of posaconazole in an oral suspension three times daily, 400 mg of fluconazole in an oral suspension once daily, or 200 mg of itraconazole in an oral solution twice daily. Patients who were unable to tolerate the oral study drug could receive IV prophylaxis at the same dose for three days or less per chemotherapy cycle. In the fluconazole or itraconazole group, the IV prophylaxis was the assigned study drug; in the posaconazole group, it was amphotericin B deoxycholate 0.3 to 0.5 mg per kilogram of body weight daily. Patients in either group were permitted to receive	N = 602 The study was conducted from August 2002 through April 2005 at 89 centers worldwide. Eligible patients aged 13 years or older who had or were anticipated to have neutropenia with an ANC ≤ 500 cells/mcl for seven days or longer resulting from remission-induction chemotherapy for newly diagnosed or the first relapse of acute myelogenous leukemia or myelodysplastic syndrome. Patients had to be able to take oral medications, although a brief period of IV therapy (less than four days) was permitted at entry into the trial.	An independent data review committee of infectious disease experts who were unaware of the treatment assignments reviewed and classified all cases of fungal infection as proven, probable, or possible, according to the consensus criteria of the European Organisation for the Research and Treatment of Cancer and the Mycoses Study Group. Endpoints: Incidence of proven or probable invasive fungal infection during the treatment phase Incidence of invasive aspergillosis	Proven or probable invasive fungal infections occurred during the treatment phase in 7 of the 304 patients (2%) in the posaconazole group and in 25 of the 298 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group = –6%; 95% confidence interval = –9.7 to –2.5; $p < 0.001$). During the 100-day period after randomization, 14 of 304 patients (5%) in the posaconazole group had a proven or probable fungal infection, as compared with 33 of 298 patients (11%) in the fluconazole or itraconazole group ($p = 0.003$).	All 602 patients in the intention-to-treat population were included in the safety evaluation. The incidence of treatment-related adverse events was similar among the treatment groups. Treatment-related prolongation of the QT or QTc interval was reported in 12 of the 304 patients (4%) receiving posaconazole, 5 of the 240 patients (2%) receiving fluconazole, and 4 of the 58 patients (7%) receiving itraconazole; the prolongation was considered to be serious in 1 patient in the posaconazole group. In this study, the investigators used their

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	amphotericin B or another systemic agent as empirical antifungal therapy for a suspected invasive fungal infection. Antifungal prophylaxis was administered with each chemotherapy cycle, starting either 24 hours after the last anthracycline dose or, in patients not receiving an anthracycline-based regimen, on the first day of chemotherapy. Prophylaxis was continued until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks from randomization, whichever came first. Patients were followed for 100 days after randomization and for 30 days after the last dose of the study drug administered during the last chemotherapy cycle.	Exclusion criteria included: an invasive fungal infection within the previous 30 days, clinically significant hepatic or renal dysfunction, an abnormal QT interval corrected for heart rate (QTc interval), a baseline Eastern Cooperative Oncology Group performance status score of more than 2 (in bed more than half of the day), a history of hypersensitivity or idiosyncratic reactions to azoles, or a requirement for medications with a potential for adverse interactions with azoles. Prospective, randomized trial	Incidence of invasive fungal infection within 100 days after randomization and treatment success (versus failure) during the treatment phase. Treatment failure was defined as the occurrence of a proven or probable invasive fungal infection; receipt of an IV study drug for four consecutive days or more, or 10 days in total; receipt of any other systemic antifungal agent for four days or more for suspected invasive fungal infection; the occurrence of an adverse event possibly or probably related to the study treatment, resulting in the discontinuation of treatment; or withdrawal from the study with no additional follow-up. Survival was evaluated 100 days after randomization, and analyses were conducted for overall survival, time to death from any cause, time to death related to fungal infection, and survival without proven	The mean (± SD) time to invasive fungal infection was 41 ± 26 days in the posaconazole group and 25 ± 26 days in the fluconazole or itraconazole group. Kaplan-Meier analysis of the time to invasive fungal infection showed a significant difference in favor of posaconazole ($p = 0.003$) Of the 304 patients in the posaconazole group, 81 (27%) received an empirical antifungal agent during the treatment phase, as did 112 of the 298 patients (38%) in the fluconazole or itraconazole group ($p = 0.004$). The analysis of the time to first use of empirical antifungal therapy during the 100-day period revealed a significant difference in favor of posaconazole over fluconazole or itraconazole ($p = 0.02$).	preferred standard azole as the comparison drug. The different dosing schedules of the three study drugs and the logistics of their IV alternatives precluded a double-blind design. To minimize the possibility of bias, an independent data review committee, whose members were unaware of the treatment assignments, examined all suspected potential invasive fungal infections to adjudicate them as proven or probable, according to international consensus criteria.

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			or probable invasive fungal infection.	Of the 304 patients in the posaconazole group, 49 (16%) died during the study period, as did 67 of 298 patients (22%) in the fluconazole or itraconazole group (p = 0.048); 44 patients (14%) and 64 patients (21%), respectively, died within 100 days. Kaplan-Meier analysis of the time to death from any cause at the end of the 100-day period after randomization showed a significant survival benefit in favor of posaconazole over fluconazole or itraconazole (p = 0.04) (Figure 1B). The relative reduction in mortality at day 100 in the posaconazole group, as compared with the fluconazole or itraconazole group, was 33%. The estimated number needed to treat with posaconazole, as compared with fluconazole or itraconazole, to prevent one death was 14 patients. Of the 116 deaths that	

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				occurred during the study, 21 were considered to be related to fungal infection: 5 (2%) that occurred in the posaconazole group and 16 (5%) in the fluconazole or itraconazole group (p = 0.01). Other causes of death were intercurrent illnesses in 20 patients (7%) in the posaconazole group and 30 patients (10%) in the fluconazole or itraconazole group, and leukemia-related complications in 24 patients (8%) and 21 patients (7%), respectively. The analysis of the time to invasive fungal infection or death also showed a significant benefit in favor of posaconazole (p = 0.01)	
Hand Hygiene					
PEP Weight of Evidence Category: Recommended for Practice					
Hillburn et al., 2003	Evaluate the effect of alcohol hand sanitizer as an infection control strategy.	Orthopedic surgical unit 498-bed acute care facility Retrospective chart review Infection data were collected for 16 months,	The use of alcohol hand sanitizer; wash hands after every five uses. Patients and families received an educational brochure on hand hygiene.	Infection by clinical findings and confirmed by laboratory A 36.1% decrease in infection rates was documented during study period (i.e., 10 months).	Single institution No randomization of patients Postdischarge surveillance was not completed.

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		and baseline data were collected for 6 months and then 10 months when alcohol hand sanitizer was made available (i.e., wall mounted and portable bottles). No conceptual model was described.	Staff education Feedback on infection rates was given monthly.	Improve compliance because alcohol hand sanitizers are easy to use and gentle on hands.	No direct observation of hand hygiene No compliance determination
Contact precautions for all patients known to be colonized or infected with multidrug resistant organisms					
PEP Weight of Evidence Category: Recommended for practice					
Srinivasan et al., 2002	Vancomycin-resistant enterococci (VRE) prevention of transmission	Mean age = 54.6 $\pm$ 16.2 Patients with at least two perirectal cultures *Gown and glove study period:* 141 patients with 64 patients colonized on admission; enrolled for 895 days 23% of patients' admission culture grew VRE *Gloves only:* Mean age = 55.0 $\pm$ 15.1 173 patients with 71 colonized; enrolled for 945 days 20% of patients' admission	Current practice studied first: gown and nonsterile, disposable gloves Change in practice studied: gloves only Private rooms and hand-washing signs Equipment such as blood pressure cuffs, thermometers, and stethoscope dedicated to patient	*Gown and glove:* 22% (11 of 49) at risk developed VRE Acquisition rate: 1.80 cases per 100 days *Glove only:* 22% (21 of 51) at risk developed VRE Acquisition rate: 3.78 cases per 100 days	Length of stay as risk factor

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		culture grew VRE Medical intensive care unit (teaching hospital) Prospective study No conceptual model was described.			
Shaikh et al., 2002	Evaluate the role of a multifaceted infection control policy in decreasing the transmission of VRE.	A tertiary hospital treating patients with cancer Hospital setting Cancer center with 417 beds Prospective cohort study No conceptual model was described.	A surveillance program was initiated: the use of empirical vancomycin was limited in febrile neutropenic patients to four specific situations. Infection control staff monitored isolation practices and educated staff and visitors.	Total incidence of VRE infections declined from 0.437 in 1,000 patient days to 0.229 in 1,000 patient days. Empiric use of vancomycin was declined.	A single hospital providing specialized cancer care A number of measures were initiated at the same time. Limited to one institution. Initiated after an outbreak. Multiple strategies were employed at once, so determining which was most effective in prevention of transmission is difficult.
Montecalvo et al., 1999	Infection measures to reduce transmission of VRE	259 patients evaluated during the use of enhanced infection control strategies and 184 patients evaluated during the use of standard infection control practices 11-room, 22-bed adult oncology unit in a 650-bed	Standard infection control versus enhanced infection control *Standard infection control:* 1. Inpatient surveillance: perianal cultures on admission and weekly 2. Hand washing before and after patient contact	VRE cultures were obtained from all 259 patients (100%) in 404 admissions to the unit during use of enhanced infection control strategies and 167 of 184 patients (91%) in 210 admissions to the unit during use of standard	Single unit where patients were not transferred No randomization 15 infection control measures were implemented simultaneously, so the

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		tertiary care hospital Prospective cohort study No conceptual model was described.	3. Contact isolation for VRE-infected and VRE-colonized patients 4. Gown and glove use for direct patient contact with VRE-infected and VRE-colonized patients 5. Consultation with infectious diseases specialists for patients with persistent fever *Enhanced infection control:* 1. Inpatient surveillance: perianal cultures on admission and weekly 2. Hand washing before and after patient contact 3. Contact isolation for VRE-colonized and VRE-infected patients 4. Gown and glove use *on* entry of rooms of VRE-infected and VRE-colonized patients 5. Consultation with infectious disease specialists when infection is first suspected, with special emphasis on reducing all use of antimicrobial agents 6. Systematic recommendation by infectious disease	infection control practices. Enhanced infection control strategies: The incidence of VRE bloodstream infections decreased significantly (1.4 patients per 1,000 days versus 3.2 patients per 1,000 days for standard group). VRE colonization was significantly reduced: 8.6 patients per 1,000 days versus 13.2 patients per 1,000 days. Compliance with enhanced strategies: 91.7% of individuals who entered rooms wore gowns and gloves.	influence of each intervention is unknown.

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			specialists to discontinue empirical vancomycin use after 72 hours 7. Systematic recommendation by infectious disease specialists to use oral metronidazole rather than oral vancomycin for *Clostridium difficile* colitis 8. Spatial separation of patients into three cohorts: VRE positive, VRE negative, and VRE unknown (VRE-unknown patients were housed on a separate unit until results of perianal culture became known.) 9. Surveillance perianal cultures taken for inpatients with cancer housed off the oncology unit 10. Gown and glove use on entry of rooms of VRE-unknown patients 11. Assignment of staff cohorts; nurses and nursing assistants assigned to VRE-positive patients or VRE-negative and VRE-unknown patients 12. Patient orientation about VRE with an		

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			explanatory brochure 13. Monitoring compliance by observational studies 14. Environmental cultures taken in VRE-positive patient rooms before and after patient discharge and room disinfection Measurements: VRE infection rates, colonization & changes in antimicrobial use		
Pre-construction plannning					
PEP Weight of Evidence Category: Likely to be effective					
Kidd, Buttner & Kressel, 2007	Infection control training program for construction workers renovating/building hospital	The University Hospital (TUH) is a tertiary care hospital in Cincinnati, Ohio. It has a level 1 trauma center, 7 intensive care units including a level 3 perinatal research center and neonatal intensive care unit and an adult burn unit. There is an average daily census of 400. Parts of the original hospital were built in 1910, 1927 and 1969. At any one time there are 4-6 major renovation projects	An infection control education program for contractors was developed and all construction workers were required to complete the training prior to working on the construction project and annually thereafter. The infection control training takes 30 minutes. The lesson plan is organized by sections that include precautions to take before, during and after the construction work. There is also an audiovisual program about Aspergillus and its transmission and	During the first 4 years of demolition and renovation, TUH had no nosocomial Aspergillus infections. In the fifth year, of construction, 2 patients who had possible hospital acquired infections were identified. An industrial hygienist was brought in to evaluate intervention and make recommendations, but nothing of concern was found. Particle sampling remained the same from pre-construction to post	Small study of one hospital initiative Case study

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		This study describes a 5 year expansion project to build a 9-story employee garage, a new post-anesthesia care unit, a new cardiothoracic intensive care unit and expansion of existing OR space to include 8 new ORs. Construction plan included demolition of 5 circa 1910 mostly unused buildings. One Infection Control Practitioner (ICP) attended a University of Minnesota Health Care Facility Construction Management Indoor Air Quality Workshop. Members of the design and construction department are engineers and architects and have attended classes on construction and infection control.	the susceptibility of immunosuppressed patients. An infection control team including the general contractor, project manager, ICP and OR nurse planner make rounds weekly or daily on all projects to monitor for compliance and answer questions. In addition, other precautions were implemented since patients could not be relocated away from the area of greatest activity. All windows adjacent to the demolition site were sealed with plastic. Prevailing wind direction was monitored and extra pre-filters were added to all air intakes. Any dust generated during demolitions was wetted	construction. Both possible nosocomial aspergillus infections occurred after a building that was connected to the hospital and share dair space began a large renovation project without using infection control prevention. Hospitals must be aware not only of what is happening inside their own facilities but also what is happening outside. ICP's must establish collegiality with contractors, architects, and maintenance and engineering personnel to produce an effective, comprehensive infection prevention atmosphere during construction and renovation	

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			down. Air curtains were added to doorways directly facing the construction. Immunosuppressed patients were notified to wear N95 protection when entering the hospital.		
Protective isolation					
PEP Weight of Evidence Category: Effectiveness not established					
Nauseef & Maki, 1981	Protective isolation versus no isolation	43 episodes of neutropenia in adults patients in a hematology-oncology unit Inpatient Randomized No conceptual model was described.	A single protective isolation (single-bed room and clean gowns, gloves, and masks for people entering room) versus standard care (two-bed room and reminder sign to wash hands)	No significant difference was found between isolated and non-isolated patients regarding the Incidence of infection, time of onset first infection, and days with fever.	
Low microbial diet for neutropenic patients					
PEP Weight of Evidence Category: Effectiveness unlikely					
DeMille, Deming, Lupinacci, & Jacobs, 2006	Adult patients (33–67 years old) who were to receive chemotherapy associated with a high degree of neutropenia and were not being treated with colony-stimulating factors (CSFs).	N = 28 23 patients completed the study. Outpatient setting Patients with acute leukemia and HIV were excluded.	1. Rates of hospital admissions for febrile episode 2. Rates of positive blood culture Questionnaires were developed to document	30% of patients were noncompliant with the neutropenic diet. No differences were found in the rate of febrile hospital admissions (per patient report and confirmed by	Reports of whether patients adhered to a neutropenic diet were done by patients via a survey at 6- and 12-week intervals, which may have decreased the accuracy of self-reported

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	Adherence to neutropenic diet and whether differences existed in rates of hospital admissions for febrile episodes and positive blood cultures between patients who adhered to the neutropenic diet and those who did not.	Descriptive pilot study that included a convenience sample of patients at one outpatient cancer center Wide range of diagnoses (except acute leukemia and HIV) Data collected at 6 weeks and 12 weeks.	demographic and medical variables as well as baseline knowledge of food safety and the neutropenic diet. Adherence to restrictions of the neutropenic diet was measured via self-report based on “yes” or “no” questions and a food-use questionnaire. The 6- and 12-week evaluations measured dietary adherence as a self-reported subjective statement with “yes” or “no” responses. Adherence was verified via eight questions targeting specific points of the food safety aspects and diet restrictions covered in the instruction. Patients’ degree of difficulty in following the diet was assessed using Likert scales with four response choices. Patients were questioned regarding hospital admissions; however, the researchers verified all admission information via chart review. The instrument designed to collect	chart review) and positive blood cultures between those patients who adhered to the neutropenic diet and those who did not.	data. No randomization of patients was done. The convenience sample compared patients who were compliant with a neutropenic diet with patients who were noncompliant. It was a small outpatient study in one setting; thus, results cannot be generalized. Content validity of the tool was established at the institution. Reliability was not tested. Of note, this study underscores the time spent for diet education, the question of appropriate content of diet education regarding food restrictions, and the difficulty adhering to diet requirements.

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			information was developed specifically for this study to assess the major aspects of the neutropenic diet for food safety and the diet instructions as given to patients. Content validity was established by review of the tool by a multidisciplinary team. A chart review was conducted post-treatment to validate self-reported medical information and verify neutropenia (i.e., ANC < 1,000/mm3). The chart review was reviewed by a multidisciplinary team for content validity. Fisher's exact test was used to analyze proportions between the groups.		
Gardner et al., 2008	Evaluation of whether a diet including fresh fruits and vegetables increased the risk of infection in adult patients with cancer who were receiving induction chemotherapy for either acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) in a protective	N = 153 patients in a single institution Patients were randomized to either a "raw group" (N = 75) that was allowed a general diet including fresh fruits and vegetables) or to a "cooked group" (N = 78) that was restricted to a low-microbial diet of all cooked food but no fresh fruit or	Endpoints for the study were pneumonia, bacteremia, major infection, fever of unknown origin, and death. The statistical design was the Bayesian multiple outcome design of Thall and Sung. The X2 or Kruskal-Wallis test was used to compare	There was no statistically significant difference in the rate of infection, pneumonia, fever of unknown origin, or overall survival between the raw and cooked groups. A significantly higher rate of bacteremia was found in the raw group; however, the authors noted that most of	The study was done at a single institution. The study was conducted with patients in a protective environment, and patients were treated routinely with prophylactic antimicrobial agents. Therefore, findings are not generalizable to outpatients, patients cared for in non-protective

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	environment	vegetables. Patients were all newly diagnosed with either AML or MDS and received induction chemotherapy in a protective environment (with a high-efficiency particulate air-filtered room). Patients remained in the protective environment from the initiation of induction chemotherapy until recovery of the absolute neutrophil count (ANC) over 500. Patients received routine antimicrobial prophylaxis with levofloxacin, valacyclovir, and an antifungal agent (itraconazole, voriconazole, or lipid amphotericin B). Granulocyte–colony-stimulating factor was not used routinely.	various pretreatment characteristics. One-third of the new patients (N = 53) refused to participate in the study and were placed in a nonrandomized group. They stayed on the low-microbial diet and were given a separate consent for chart review.	the organisms responsible for the baceteremia were not of enteric origin. Median age of the patients in the raw group was 63. Median age of the patients in the cooked group was 64. The most frequent chemotherapy used was cytarabine. The median number of days with an ANC less than 500/mcl was 20 days in the cooked group and 21 days in the raw group. The median number of days with an ANC less than 100/mcl was 15 in the cooked group and 16 in the raw group. Major infection rates: Raw group: 35% Cooked group: 29% ($p = 0.60$) Pneumonia rates: Raw group: 5% Cooked group: 15% ($p = 0.06$) Bacteremia or fungemia rates: Raw group: 23% Cooked group: 9%	envorinments, or patients not treated with prophylactic antimicrobial agents. The rates of infection and death were the same between study groups; however, the rate of bacteremia was significantly higher in the raw group. Although the incidence of bacteremia was higher in the raw group, the authors reported that a substantial part of the difference reflected isolation of organisms not resident in the gut; the presence of such organisms would not be expected to be influenced by cooking of fruits and vegetables. Additionally, the incidence of fever of unknown origin was higher in the cooked group, suggesting that some cases of bacteremia in the cooked group were not identified. One strength of the study is that the sample was a population of high-risk patients who had an ANC

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				(p = 0.03) Fever of unknown origin rates: Raw group: 36% Cooked group: 51% (p = 0.07) Rate of infection or fever of unknown origin: Raw group: 76% Cooked group: 87% (p = 0.09) No significant difference existed in the rate of enteric organisms cultured from blood in either group. (p = 0.12). Survival rates: Raw group: 61% Cooked group: 56% Non-randomized: 64% Survival in all three groups was as expected in older patients with newly diagnosed AML or MDS. Conclusions: A diet that includes raw fruits and vegetables did not increase the risk of infection or death in patients with MDS or AML treated with remission induction chemotherapy in a protective environment when compared to a diet	less than 500/mcl for a median of 20 days. In comparison, patients with solid tumors treated with chemotherapy are at low risk for infection, and the patients that experience neutropenia generally have an ANC less than 500/mcl less than seven days. Because this study demonstrated an absence of efficacy of the low-microbial diet in high-risk patients; it is unlikely to be of benefit in low-risk patients with a much shorter duration of neutropenia. However, further research is warranted to confirm the findings in other populations of neutropenic patients.

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				that restricted raw fruits and vegetables.	
Mank & Davies, 2008	Examination of low bacterial diet (LBD) practices	Questionnaire to members of the European Blood and Marrow Transplant (EBMT) Nurses group Members were first accessed through the EBMT congress in 2004. Questions were administered to each delegate during educational sessions. Following the congress, an analysis of completed questionnaires was undertaken and the missing centers were identified using the EBMT database. The questionnaire was piloted with the Dutch Stem Cell Transplantation Group so that any problems or weaknesses could be identified and addressed.	18 questions were developed with the aim of providing data on existing guidelines, patient information, reference points for starting and stopping LBDs, and dietary restrictions. Restrictions were divided into three categories: completely forbidden, product restrictions only, and process restrictions only. Product restrictions are when some ingredient or some of the product is forbidden, such as nuts in a candy bar. Process restrictions are when the food item can be eaten only in a particular way, such as when cooked. 18 products were chosen according to a brief literature search in which	248 questionnaires were distributed; 108 people responded (44%). Results came from 29 countries, 20 European. Other countries: 1 Canada, 2 Brazil, 1 South Africa, 2 Australia, and 1 New Zealand Most were completed by nurses: 74 (69%). Other professionals included: Transplant coordinators: 21 (19.4%) Dieticians: 8 (7.4%) Others: 4 (3.7%) 62 (57%) worked on a ward with adult patients. Number of stem cell transplants performed at each center was < 50 for 51 centers (47%) 51-100 for 37 centers (43%).	Questionnaire Self-selection resulting from survey Response rate of 44% Possibility exists that cultural and geographical differences may have an impact on local practice.

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			specific products thought to be problematic were identified. Products included were: Bread; breakfast cereals; meat and poultry; butter or margarine; jam, marmalade, and peanut butter; bottled water; tap water; cold drinks such as juices or soft drinks; fresh fruit; raisins, nuts, and other dried fruits; raw vegetables; cheese; spices; wrapped ice cream; foods brought by visitors; hot meals prepared at home; candy and chocolate; and alcoholic drinks.	Not all centers had diet guidelines. 95 (88%) used diet guidelines during hospitalization. 79 (73%) had guidelines following discharge. 76 (70%) had a permanent dietician on the unit. One hospital used no LBD. 3 used very liberal LBD. 37 (34%) start LBD for auto Hematopoietic Cell Transplant (HCT) and 33 (31%) for allo HCT upon admission. 25 (23%) start LBD for auto HCT and 23 (21%) for allo HCT at the start of chemotherapy. 27 (25%) start LBD for auto HCT and 20 (18.5%) start LBD for allo HCT based on blood counts. However, the parameters for blood counts varied widely. 39 (36%) stopped LBD for	

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				auto HCT and 24 (22%) for allo HCT based on blood counts. 22 (20%) stopped LBD for auto HCT and 38 (35%) for allo HCT based on other conditions, usually based on time periods such as days or weeks following chemotherapy. 48 (44%) imposed restrictions on all 18 products. Bread and bottled water were the least restricted; more than 50% did not restrict them at all. 96 (89%) restricted fruit. 95 (88%) restricted cheese. Both held the most stringent restrictions. Meat and poultry 53 (49%) and fresh fruit 61 (57%) have the highest number of process restrictions. Food brought into the hospital by visitors was found to be frequently	

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				restricted 88 (81%), especially for process restrictions 50 (46%). Some respondents reported no restrictions for some products, whereas other centers forbade them completely: raisins, nuts, and dried fruits with no restrictions, 25 (23%); forbidden, 46 (43%). Tap water was reported as having no restrictions, 24 (22%); forbidden, 41 (38%). 88% have guidelines, but there are enormous differences in the guidelines themselves and the way in which they are implemented. 10% of centers have no guidelines for hospitalized patients. Evidence supporting LBD is unsubstantiated.	
Moody et al., 2006	Pediatric patients (aged 1–21 years) undergoing myelosuppressive chemotherapy were randomized to receive a	N = 19 Prospective, randomized, controlled pilot study at two hospitals in New York.	Infection was measured with hospital admission data for febrile neutropenia. Localized infection (along with an ANC < 500	No statistically significant differences in infection was found between the two groups. Four patients on each arm	Small sample size. Difficulty adhering to the neutropenic diet was reported. Adherence measured by

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	neutropenic diet or a diet based on the U.S. Food and Drug Administration (FDA) food safety guidelines (emphasis on safe handling and cooking). Patients were enrolled during one cycle of chemotherapy.	Purpose of the study was to demonstrate a safe and feasible methodology to evaluate the infection rate in pediatric patients with cancer randomized to the neutropenic diet or the FDA-approved food safety guidelines. Primary outcome was febrile neutropenia. Secondary outcome was adherence and diet tolerability. Groups were matched on all variables except history of febrile neutropenia.	cells/mm^3) also was included. Dietary adherence measured by 24-hour diet recall. Student t test measured differences between the groups.	developed febrile neutropenia. Adherence rate was 94% for neutropenic diet and 100% for FDA-approved food safety guidelines.	24-hour diet recall.
Smith & Besser, 2000	Mailed survey regarding institutional practices related to dietary restrictions for patients with neutropenia (when initiated and discontinued and existing restrictions)	Convenience sample 156 institutions of 400 belonging to the Association of Community Cancer Centers responded (response rate = 39%). Mean number of hospital beds = 309 (range 81–500) Affiliations: University = 35% Cooperative group = 20% Return addresses indicated > 38 states were	Neutropenic diet Neutropenia defined for respondents ANC < 1,000 = 42% ANC< 500 = 43% Other ANC =15%	Recommendations varied from none to extensive. 78% (n = 120) restricted diets for neutropenic patients. Of these, 43% restricted diets when the ANC was < 1000 and 46% when the ANC was < 500. 83% restricted diets only when patients were neutropenic, rather than during the entire duration of their chemotherapy. A significant relationship (p = 0.0007) existed between	Excluded bone marrow transplant recipients Convenience sample Inconsistencies were found in the literature, and research was lacking. The questionnaire was based on the literature review; content validity and reliability were not established. Survey self-report, which did not allow for

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		represented. 156 institutions were queried. Descriptive survey No conceptual model was described.		size of institution and dietary restrictions; institutions with > 251 beds restricted diets (89%) versus those with < 250 beds (71%). The most commonly restricted foods were fresh fruits (92%), fresh vegetables (95%), raw eggs (74%), wine (39%), and beer (40%). The role of diet in the development of infection is unclear.	opportunities for clarification if needed No questions regarding pediatric versus adult patients Decreased costs were noted if dietary restrictions were unnecessary.
Van Tiel et al., 2007	Adult patients with acute leukemia receiving remission induction chemotherapy. Patients received either antibacterial prophylaxis (AP) and low-microbial diet (LBD) or AP and normal hospital diet (NHD) to prevent infections.	N = 20 (5 women and 15 men) All patients with acute leukemia undergoing remission induction chemotherapy Randomized, controlled pilot study Patients were randomized into two groups. 1. Patients receiving antibiotic prophylaxis (AP) and low-bacterial diet (LBD) 2. Patients receiving AP and normal hospital diet (NHD).	Infection was measured by gastrointestinal tract colonization with yeast or gram-negative bacilli or fever > 38° C. Stool was measured daily for bacterial colonization. A student t test compared degree of colonization between the two groups. Differences at cycle-specific points in time were evaluated with a multivariate analysis of variance (MANOVA). Differences in temperature were measured by the	No statistically significant differences were found between the two groups for rates of infection.	The small pilot study and sample size were inadequate to observe significant differences between the study groups. The study did not measure whether patients were adherent to their assigned diets. Randomization could not create two equal groups. Patients received AP. Results cannot be generalized because of the small sample size.

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		AP included ciprofloxacin 500 mg every 12 hours and oral fluconazole 50 mg every 24 hours and was started before initiation of chemotherapy and discontinued when leukocyte counts recovered to 1000/mm^3 or higher.	Fisher's exact test.		
Branda et al., 2004	Questionnaire regarding the use of dietary supplements; blood samples were obtained.	N = 68 women enrolled with 49 questionnaires completed 68 women with histologically proven breast carcinoma were enrolled on this study and 49 of them submitted questionnaires Fifty-four patients received doxorubicin or cyclophos-phamide; three patients received doxorubicin with docetaxel; six patients received cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU); two patients received single-agent doxorubicin; and three patients received a single-agent taxane. Mean age= 48.1 years	14 women (29%) did not take dietary supplements, 8 (16%) took 1 supplement, 18 (37%) took 2–5 supplements, 5 (10%) took 6–10 supplements, and 4 (8%) took more than 10 supplements. Supplements taken: *Vitamins:* Multivitamin: n = 23 (47%) Vitamin A: n = 5 (10%) Folic acid: n = 3 (6%) Vitamin B_{12}: n = 2 (4%) Vitamin B complex: n = 3 (6%) Vitamin C: n = 11 (22%) Vitamin D: n = 3 (6%) Vitamin E: n = 18 (37%) *Minerals:* Mineral complex: n= 3 (6%) Calcium: n = 13 (27%) Iron: n = 1 (2%)	35 of 49 subjects took a combined total of 165 supplements. No significant difference was found in the nadir ANC between the supplement group and the no-supplement group, although the supplement group had a significantly lower decrease in ANC from baseline ($p < 0.01$). Compared with the absence of multivitamin or vitamin E supplement use, multivitamin or vitamin E supplement use was associated with more grade 0–1 neutropenia (30% multivitamin and 22% vitamin E versus 7% no supplement) and less grade 3 neutropenia (26%	79 subjects were enrolled, 68 met inclusion criteria, and 49 completed questionnaire Pilot study and small sample size Single institution Heterogeneity of supplements used Heterogeneity of chemotherapeutic regimens used Nonrandomized

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		(range 30–75) Outpatient (inferred) Pilot study A descriptive questionnaire was used, and the following blood samples were obtained: weekly complete blood counts with differential during the first cycle of chemotherapy (typically three to four weeks) and serum vitamin B_{12} and folate levels before the first and second cycle of chemotherapy No conceptual model was described.	Magnesium: n = 2 (4%) Selenium: n = 3 (6%) Zinc: n = 1 (2%) *Nutraceuticals:* Gingko: n = 7 (12%) Echinacea: n = 3 (6%) Coenzyme Q: n = 8 (14%) Pectin: n = 2 (3%) Glutamine: n = 3 (5%) Other: n = 18 (37%) Toxicity assessment: Neutropenia was analyzed in three ways: (a) The difference between the neutrophil count immediately before chemotherapy and the nadir count during the first cycle, (b) the nadir ANC, and (c) categorization of neutrophil counts by grade as follows: grade 4 ANC ≤ 100, grade 3 ANC = 100–500, grade 2 ANC = 500–1,000, and grade 0 or 1 ANC > 1,000. Mucositis: Physician-graded according to National Cancer Institute Common Toxicity Criteria version 2.0	multivitamin and 33% vitamin E versus 57% no supplement). However, multivitamin or vitamin E use did not affect the nadir ANC. High serum folate exacerbated a decrease in nadir ANC from baseline but did not affect overall nadir ANC. Mucositis: 51 subjects had grade 0, 11 had grade 1, and 6 had grade 2 or 3 No association was found between oral mucositis and initial ANC, nadir ANC, age, vitamin B_{12} level, or folate level.	

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Evidence Table

(Literature search completed through May 2008)