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Nystatin prophylaxis and treatment in severely immunodepressed patients (Review)

Gøtzsche PC, Johansen HK

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[Intervention Review]

Nystatin prophylaxis and treatment in severely immunodepressed patients

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ABSTRACT

Background

Nystatin is sometimes used prophylactically in patients with severe immunodeficiency or in the treatment of fungal infection in such patients, although its effect seems to be equivocal.

Objectives

To study whether nystatin decreases morbidity and mortality when given prophylactically or therapeutically to patients with severe immunodeficiency.

Search methods

We searched PubMed from 1966 to 7 July 2014 and the reference lists of identified articles.

Selection criteria

Randomised clinical trials comparing nystatin with placebo, an untreated control group, fluconazole or amphotericin B.

Data collection and analysis

Data on mortality, invasive fungal infection and colonisation were independently extracted by both authors. A random-effects model was used unless the P value was greater than 0.10 for the test of heterogeneity.

Main results

We included 14 trials (1569 patients). The drugs were given prophylactically in 12 trials and as treatment in two. Eleven trials were in acute leukaemia, solid cancer, or bone marrow recipients; one in liver transplant patients; one in critically ill surgical and trauma patients; and one in AIDS patients. Nystatin was compared with placebo in three trials, with fluconazole in 10, and amphotericin B in one; the dose varied from 0.8 MIE to 72 MIE daily and was 2 mg/kg/d in a liposomal formulation. The effect of nystatin was similar to that of placebo on fungal colonisation (relative risk (RR) 0.85, 95% confidence interval (CI) 0.65 to 1.13). There was no statistically significant difference between fluconazole and nystatin on mortality (RR 0.75, 95% CI 0.54 to 1.03) whereas fluconazole was more effective in preventing invasive fungal infection (RR 0.40, 95% CI 0.17 to 0.93) and colonisation (RR 0.50, 95% CI 0.36 to 0.68). There were no proven fungal infections in a small trial that compared amphotericin B with liposomal nystatin. The results were very similar if the three studies that were not performed in cancer patients were excluded. For the 2011 and 2014 updates no additional trials were identified for inclusion.

Authors' conclusions

Nystatin cannot be recommended for prophylaxis or the treatment of Candida infections in immunodepressed patients.

PLAIN LANGUAGE SUMMARY

Prevention and treatment of fungal infections with nystatin in severely immunodepressed patients

People on chemotherapy for cancer, receiving a transplant or with AIDS are at risk of fungal infections. These infections can be life-threatening, especially when they spread throughout the body. Nystatin is sometimes given as a routine preventive measure or as treatment in these patients. The review found that nystatin was no better than placebo (no treatment).

BACKGROUND

Nystatin is often used for treatment of oral candidiasis in otherwise healthy patients, for example in patients with candidiasis after antibiotic therapy or in patients with denture stomatitis. The drug is also sometimes used prophylactically in patients with severe immunodeficiency, for example in patients undergoing antileukaemic chemotherapy or bone marrow transplantation or in patients with AIDS. We reviewed the relevant clinical trials in patients with severe immunodeficiency.

OBJECTIVES

To study whether nystatin decreases morbidity and mortality when given prophylactically or therapeutically to patients with severe immunodeficiency.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials, irrespective of language, which compared nystatin with placebo, an untreated control group, fluconazole or amphotericin B were eligible. Fluconazole and amphotericin B were chosen as active comparators as in a previous Cochrane review of placebo controlled trials (Gøtzsche 1997; Gøtzsche 2002) they appeared to be the most effective antifungal agents.

Types of participants

Patients with severe immunodeficiency predisposing to fungal infection, for example patients undergoing antileukaemic chemotherapy or bone marrow transplantation and patients with AIDS.

Types of interventions

Experimental: nystatin. Control: placebo, no treatment, fluconazole or amphotericin B.

Types of outcome measures

- Mortality
- Invasive fungal infection (defined as a positive blood culture, oesophageal candidiasis, lung infection or microscopically confirmed deep tissue involvement)
- Colonisation
- Harms

Search methods for identification of studies

Electronic searches

We searched PubMed from 1966 to 7 July 2014 and the reference lists of identified articles.

The search strategy used is in Appendix 1.

The search strategies have been developed and executed by the author team.

Searching other resources

This has not been carried out since 2007 as we have not found it worthwhile.

Data collection and analysis

Data extraction and management

Decisions on which trials to include and which variables to use when a number of options were available for the same outcome were based on the methods sections of the trials. Details on diagnosis, drug, dose, randomisation and blinding methods, number of randomised patients, number of patients excluded from analysis, deaths, invasive fungal infections and colonisation were independently extracted by both authors; differences in the data extracted were resolved by consensus.

We defined invasive fungal infection as a positive blood culture, oesophageal candidiasis, lung infection or microscopically confirmed deep tissue infection (Gøtzsche 2002). We excluded cases of oropharyngeal and vulvovaginal candidiasis, skin infections, Candida in the urine and vaguely described infections.

Data synthesis

The outcomes were meta-analysed as relative risks with the Mantel-Haenszel technique. Since heterogeneity of the studies was expected because of various designs, diagnoses, drugs, doses and routes of administration, and criteria for fungal invasion and colonisation a random-effects model was used. A fixed-effect model analysis was preferred, however, if the P value was greater than 0.10 for the test of heterogeneity. Ninety-five per cent confidence intervals were presented.

RESULTS

Description of studies

We identified 18 potentially relevant reports. Four were subsequently excluded. A trial in which only 12 patients received nystatin failed due to serious problems with compliance (Hoppe 1995); another reported only the number of 'Candida-free' days (which was 18 on both nystatin and on placebo) (Williams 1977); the third report was a duplicate publication (Ellis 1994); and in the fourth trial, which compared nystatin with amphotericin B (Epstein 2004), all 40 patients received systemic fluconazole 200 mg/d, which is an effective treatment. Of the 14 included trials 3 were published as abstracts only (Feusner 1994; Powles 1999; Tian 1997).

The drugs were given prophylactically in 12 trials and as treatment in 2 (Flynn 1995; Pons 1997). Acute leukaemia was the most common disease in eight trials; two trials concerned exclusively (Feusner 1994) or mainly (Flynn 1995) patients with cancer, one mainly patients receiving a bone marrow transplant (Powles 1999), one patients receiving a liver transplant (Lumbreras 1996), one critically ill surgical and trauma patients (Savino 1994), and one AIDS patients (Pons 1997). Nystatin was compared with placebo or no treatment in 3 trials, with fluconazole in 10, and with amphotericin B in one; all drugs were given orally apart from the amphotericin B trial (Powles 1999). The daily dose of nystatin in adults varied from 0.8 MIE to 72 MIE daily, and was 2 mg/kg/d in a liposomal formulation. In three trials the participants were children (Feusner 1994; Flynn 1995; Groll 1997). Length of follow-up was stated in only three trials (Ellis 1994; Lumbreras 1996; Powles 1999). Although one of the trials was described as a two-armed study (Groll 1997), 18 of the patients were also included in a report of a three-armed study (Ninane 1994). We have previously drawn

attention to this curious discrepancy but it has not been explained (Johansen 1999).

For the 2011 and 2014 updates no additional trials were identified for inclusion.

Risk of bias in included studies

We adopted broad quality assessment criteria and considered the risk of bias to be be low if the randomisation method was concealed, for example if central randomisation, use of sealed envelopes, a code provided by a pharmacy or a company was described; and if the generation of the allocation sequence was adequate (for example random numbers) and the trial was placebo controlled and blinded. Concealment of treatment allocation was reported in three trials (Ellis 1994; Flynn 1995; Savino 1994). Blinding was reported in five trials; the control group received saline in one trial (Epstein 1992), the double-dummy technique was used in one trial (Young 1999), and the assessors were blinded in three trials (Ellis 1994; Flynn 1995; Pons 1997). Losses to follow-up and exclusions were reasonably low apart from one trial (Young 1999) where the only reliable data were those for mortality (Characteristics of included studies).

Effects of interventions

None of the three placebo-controlled trials reported on deaths or on invasive fungal infection according to our criteria. One trial reported five cases of sepsis on nystatin and two on placebo but the definition of sepsis included positive cultures from at least three sites (Savino 1994). The effect of nystatin was similar to that of placebo on fungal colonisation; the total number of colonisations on nystatin was 53 out of 164 patients while it was 57 out of 147 on placebo (relative risk (RR) 0.85, 95% confidence interval (CI) 0.65 to 1.13).

There was no statistically significant difference between fluconazole and nystatin on mortality (RR 0.75, 95% CI 0.54 to 1.03) whereas fluconazole was considerably more effective in preventing invasive fungal infection (RR 0.40, 95% CI 0.17 to 0.93) and colonisation (RR 0.50, 95% CI 0.36 to 0.68). There was marked heterogeneity for colonisation (P value < 0.001), which was driven by an unusually large effect of fluconazole in one of the two treatment trials in which the patients had oropharyngeal thrush (Flynn 1995) and a very small effect in one of the prophylactic trials (Groll 1997). The heterogeneity was probably caused by the lack of a consistent definition of colonisation. If these two studies were excluded the heterogeneity disappeared whereas the RR was virtually the same as before (RR 0.48, 95% CI 0.39 to 0.58). The results were also similar for all three outcomes if the studies that were not performed in cancer patients were excluded. There were no proven fungal infections in a small trial that compared amphotericin B with liposomal nystatin (4 out of 15 versus 2 out of 16 patients died) (Powles 1999).

The results were similar for the trials with adequate concealment of allocation, but the power was low for a comparison with those trials that did not provide information on the randomisation method.

The reporting of harms was variable from trial to trial, and some trials reported no data at all (Table 1). Treatment discontinuations were most commonly caused by nausea, vomiting, and liver enzyme increases; and oral administration of nystatin was described as difficult in two trials.

DISCUSSION

Nystatin is an old drug which is still frequently used for the prophylaxis and treatment of Candida infections. However, it is widely recognized as being a relatively ineffective drug. Nystatin is almost insoluble and it is not recommended for use in cancer patients with neutropenia (Working Party 1995). We could confirm this recommendation, at least in patients with severe immunodeficiency, which was the type of patients we included in this review. Nystatin was no better than placebo and this finding is strengthened by the fact that the difference between fluconazole and nystatin was very similar to the difference between fluconazole and placebo, which we have reported on previously (Gøtzsche 1997; Gøtzsche 2002). Whether nystatin is effective in patients who are not immunodepressed is a different matter that needs a separate review.

AUTHORS' CONCLUSIONS

Implications for practice

The effect of nystatin given orally to immunodepressed patients was no better than that of placebo, whereas it was inferior to the effect of fluconazole. Nystatin cannot be recommended for prophylaxis or treatment of Candida infections in immunodepressed patients.

Implications for research

There seems to be little scope for further trials of nystatin given orally to immunodepressed patients since more effective antifungal agents exist, and since the effect of nystatin was at placebo level.

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REFERENCES

References to studies included in this review

Buchanan 1985 *{published data only}*

* Buchanan AG, Riben PD, Rayner EN, Parker SE, Ronald AR, Louie TJ. Nystatin prophylaxis of fungal colonization and infection in granulocytopenic patients: correlation of colonization and clinical outcome. *Clinical and Investigative Medicine* 1985;**8**:139-47.

Egger 1995 *{published data only}*

* Egger T, Gratwohl A, Tichelli A, Uhr M, Stebler Gysi C, Passweg J, et al. Comparison of fluconazole with oral polyenes in the prevention of fungal infections in neutropenic patients. A prospective, randomized, single-center study. *Supportive Care in Cancer* 1995;**3**:139-46.

Ellis 1994 *{published data only}*

* Ellis ME, Clink H, Ernst P, Halim MA, Padmos A, Spence D, et al. Controlled study of fluconazole in the prevention of fungal infections in neutropenic patients with haematological malignancies and bone marrow transplant recipients. *European Journal of Clinical Microbiology & Infectious Diseases* 1994;**13**:3-11.

Ellis ME, Qadri SM, Spence D, Halim MA, Ernst P, Clink H, et al. The effect of fluconazole as prophylaxis for neutropenic patients on the isolation of Candida spp. from surveillance cultures. *The Journal of Antimicrobial Chemotherapy* 1994;**33**:1223-8.

Epstein 1992 *{published data only}*

* Epstein JB, Vickars L, Spinelli J, Reece D. Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. *Oral Surgery, Oral Medicine, and Oral Pathology* 1992;**73**:682-9.

Feusner 1994 *{published data only}*

* Feusner J, Robinson P, Seibel N, Reaman G, Waskerwitz M, Thompson C. Fluconazole (FLU) vs nystatin (NYS) for the prevention of fungal infection in neutropenic children receiving cytotoxic chemotherapy. *Proceedings of the Annual Meeting of the American Society of Clinical Oncology* 1994;**13**:444 (Abstract A1533).

Flynn 1995 *{published data only}*

* Flynn PM, Cunningham CK, Kerkering T, San Jorge AR, Peters VB, Pitel PA, et al. Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. The Multicenter Fluconazole Study Group. *The Journal of Paediatrics* 1995;**127**:322-8.

Groll 1997 *{published data only}*

* Groll AH, Just-Nuebling G, Kurz M, Mueller C, Nowak-Goettl U, Schwabe D, et al. Fluconazole versus nystatin in the prevention of candida infections in children and adolescents undergoing remission induction or consolidation chemotherapy for cancer. *The Journal of Antimicrobial Chemotherapy* 1997;**40**:855-62.

Lumbreras 1996 *{published data only}*

* Lumbreras C, Cuervas-Mons V, Jara P, del Palacio A, Turrion VS, Barrios C, et al. Randomized trial of fluconazole versus nystatin for the prophylaxis of Candida infection following liver transplantation. *The Journal of Infectious Diseases* 1996;**174**:583-8.

Pons 1997 *{published data only}*

* Pons V, Greenspan D, Lozada-Nur F, McPhail L, Gallant JR, Tunkel A, et al. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clinical Infectious Diseases* 1997;**24**:1204-7.

Powles 1999 *{published data only}*

* Powles R, Kulkarni S, Treleaven J, Hobbs K, Sirohi B, Bhagwati N, et al. Phase III randomized trial of Nyotran (liposomal nystatin) or amphotericin B for the empiric antifungal therapy in febrile neutropenic patients [abstract]. 41st Annual Meeting of the American Society of Hematology. *Blood* 1999;**94 (10 Suppl 1)**:342a.

Savino 1994 *{published data only}*

* Savino JA, Agarwal N, Wry P, Policastro A, Cerabona T, Austria L. Routine prophylactic antifungal agents (clotrimazole, ketoconazole, and nystatin) in nontransplant/nonburned critically ill surgical and trauma patients. *The Journal of Trauma* 1994;**36**:20-5.

Tian 1997 *{published data only}*

* Tian D, Jian H, Cui X, et al. Prospective study of fluconazole in the prevention of fungal infections in neutropenic patients with acute leukemia and non-Hodgkins lymphoma. 20th International Congress of Chemotherapy, June 29 to July 3 1997, Sydney, Australia. 1997:87 abstract no 3246.

van Delden 1995 *{published data only}*

* Van Delden C, Lew DP, Chapuis B, Rohner P, Hirschel B. Antifungal prophylaxis in severely neutropenic patients: How much fluconazole is necessary?. *Journal of Clinical Microbiology and Infection* 1995;**1(1)**:24-30.

Young 1999 *{published data only}*

* Young GA, Bosly A, Gibbs DL, Durrant S. A double-blind comparison of fluconazole and nystatin in the prevention of candidiasis in patients with leukaemia. Antifungal Prophylaxis Study Group. *European Journal of Cancer* 1999;**35**(8):1208-13.

References to studies excluded from this review

Carpentieri 1978 *{published data only}*

Carpentieri U, Haggard ME, Lockhart LH, Gustavson LP, Box QT, West EF. Clinical experience in prevention of candidiasis by nystatin in children with acute lymphocytic leukemia. *The Journal of Pediatrics* 1978;**92**:593-5.

DeGregorio 1982 *{published data only}*

DeGregorio MW, Lee WM, Ries CA. Candida infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and

relationship between oropharyngeal and systemic candidiasis. *Cancer* 1982;**50**:2780-4.

Epstein 2004 *{published data only}*

Epstein JB, Truelove EL, Hanson-Huggins K, Mancl LA, Chen A, Press OW, et al. Topical polyene antifungals in hematopoietic cell transplant patients: tolerability and efficacy. *Supportive Care in Cancer* 2004;**12(7)**:517-25.

Hoppe 1995 *{published data only}*

Hoppe JE, Friess D, Niethammer D. Orointestinal yeast colonization of paediatric oncologic patients during antifungal prophylaxis: results of quantitative culture and Candida serology and comparison of three polyenes. *Mycoses* 1995;**38**:41-9.

Williams 1977 *{published data only}*

Williams C, Whitehouse JM, Lister TA, Wrigley PF. Oral anticandidal prophylaxis in patients undergoing chemotherapy for acute leukemia. *Medical and Pediatric Oncology* 1977;**3**:275-80.

Additional references

Gøtzsche 1997

Gøtzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. *BMJ* 1997;**314**:1238-44.

Gøtzsche 2002

Gøtzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [DOI: 10.1002/14651858.CD000026]

Ninane 1994

Ninane J. A multicentre study of fluconazole versus oral polyenes in the prevention of fungal infection in children with hematological or oncological malignancies. Multicentre Study Group. *European Journal of Clinical Microbiology and Infectious Diseases* 1994;**13**:330-7.

Working Party 1995

Working Party of the British Society for Antimicrobial Chemotherapy. Antifungal drug chemotherapy. Antifungal drug susceptibility testing. *The Journal of Antimicrobial Chemotherapy* 1995;**36**:899-909.

References to other published versions of this review

Gøtzsche 2001

Gøtzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD002033]

Johansen 1999

Johansen HK, Gøtzsche PC. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA* 1999;**282**:1752-9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Buchanan 1985

Methods	Allocation concealment: NA Blinding: none
Participants	78 patients with acute leukaemia, prophylactic Excluded: NA
Interventions	Experimental: nystatin suspension 1 MIE x 6 Control: no treatment
Outcomes	Colonisation Infections
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Buchanan 1985 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Egger 1995

Methods	Allocation concealment: NA Blinding: none
Participants	90 patients with acute leukaemia, prophylactic Excluded: 1
Interventions	Experimental: fluconazole 400 mg orally or iv once daily Control: nystatin suspension 24 MIE x 3 and miconazole inhalations x 3
Outcomes	Colonisation Infections Use of escape drug
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Ellis 1994

Methods	Allocation concealment: computer generated code at pharmacy Blinding: observer and analysis
Participants	94 patients with acute leukaemia, prophylactic Excluded: 4
Interventions	Experimental: fluconazole 200 mg orally once daily Control: mouthwash with nystatin 0.5 MIE, benadryl elixir and cepacol x 4 and clotrimazole troches 10 mg x 2
Outcomes	Colonisation Infections Deaths
Notes	

Ellis 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Epstein 1992

Methods	Allocation concealment: NA Blinding: saline as control treatment
Participants	99 patients with acute leukaemia, prophylactic Excluded: 13
Interventions	Experimental: nystatin suspension 1.5 MIE x 4 Control: saline
Outcomes	Colonisation Oral mucositis
Notes	Factorial design

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Feusner 1994

Methods	Allocation concealment: NA Blinding: NA
Participants	178 children with neutropenia after chemotherapy, prophylactic Excluded: NA
Interventions	Experimental: fluconazole 6 mg/kg/d Control: nystatin 0.4 MIE x 4
Outcomes	Colonisation Infections
Notes	Published as abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Flynn 1995

Methods	Allocation concealment: computer generated code held by pharmacist Blinding: observer
Participants	186 children with immunodeficiency (92 cancer, 64 HIV, 30 immunosuppressive disorder and/or therapy) and oral candidiasis, treatment Excluded: 27
Interventions	Experimental: fluconazole suspension 2 mg/kg/d Control: nystatin suspension 0.4 MIE x 4
Outcomes	Colonisation Deaths Clinical symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Groll 1997

Methods	Allocation concealment: NA Blinding: none
Participants	60 children with acute leukaemia, prophylactic Excluded: 10
Interventions	Experimental: fluconazole suspension 3 mg/kg/d Control: nystatin suspension 0.05 MIE/kg/d
Outcomes	Colonisation Infections Deaths
Notes	Although this is described as a two-armed study, 18 of the patients were also included in a report of a three-armed study (Ninane 1994). This discrepancy has not been explained

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias)	High risk	

Groll 1997 *(Continued)*

All outcomes

Lumbreras 1996

Methods	Allocation concealment: NA Blinding: none
Participants	143 patients with a liver transplant, prophylactic Excluded: none
Interventions	Experimental: fluconazole capsule 100 mg daily Control: nystatin suspension 1 MIE x 4
Outcomes	Colonisation Infections Deaths
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Pons 1997

Methods	Allocation concealment: NA Blinding: observer
Participants	167 patients with AIDS and oropharyngeal candidiasis, treatment Excluded: 29
Interventions	Experimental: fluconazole suspension 100 mg daily Control: nystatin suspension 0.5 MIE x 4
Outcomes	Colonisation Deaths Clinical cure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pons 1997 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk

Powles 1999

Methods	Allocation concealment: NA Blinding: NA
Participants	31 cancer patients with neutropenia, mostly bone marrow recipients, empiric Excluded: four patients were "non-evaluable"
Interventions	Experimental: amphotericin B 0.8 mg/kg/d iv over 4 h Control: liposomal nystatin 2 mg/kg/d i.v. over 2 h
Outcomes	Normalisation of temperature Tolerability Infections Deaths
Notes	Patients completing 5 days of treatment were "evaluable". No patients developed proven fungal infection. Not clear how many died

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Savino 1994

Methods	Allocation concealment: sealed envelopes drawn sequentially Blinding: none
Participants	147 critically ill surgical and trauma patients, prophylactic Excluded: none
Interventions	Experimental: nystatin 2 MIE x 4 Control: no treatment
Outcomes	Colonisation Infections Deaths
Notes	Data on infections and deaths were not divided on treatment groups according to our definitions. Four-armed study, with ketoconazole and clotrimazole in addition

Risk of bias

Bias	Authors' judgement	Support for judgement

Savino 1994 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	

Tian 1997

Methods	Allocation concealment: NA Blinding: NA
Participants	80 patients with acute leukaemia and other haematologic malignancies, prophylactic Excluded: NA
Interventions	Experimental: fluconazole 50 mg daily Control: nystatin 0.5 MIE x 3
Outcomes	Colonisation Infections
Notes	Abstract, few data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

van Delden 1995

Methods	Allocation concealment: NA Blinding: none
Participants	74 cancer patients with neutropenia, mostly leukaemia, prophylactic Excluded: 1 in fluconazole group, 6 in nystatin group
Interventions	Experimental: fluconazole 100 mg daily as capsule (iv if not tolerated) Control: nystatin 0.8 MIE/d as solution
Outcomes	Colonisation Infections Deaths Use of escape drug
Notes	Trial stopped prematurely because of other trial results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

van Delden 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Young 1999

Methods	Allocation concealment: NA Blinding: double-blind (double-dummy technique) Patients could be enrolled more than once (no data given)
Participants	164 leukaemic patients with neutropenia after chemotherapy, prophylactic Excluded: 1 from mortality analysis, 55 from other efficacy analyses
Interventions	Experimental: fluconazole 200 mg daily Control: nystatin 6 MIE daily
Outcomes	Colonisation Infections Deaths
Notes	The validity of this trial is greatly reduced by the many exclusions, some of which appear rather dubious, eg 12 versus 0 patients were excluded because of "incorrect dosing" although all patients recieved the same doses because of the double-dummy technique. Intention-to-treat analysis rendered significant findings non-significant

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	

NA: not available

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carpentieri 1978	Not a randomised trial
DeGregorio 1982	Not a randomised trial
Epstein 2004	All 40 patients received systemic fluconazole, 200 mg/d, which is an effective treatment
Hoppe 1995	Failed because of serious compliance problems

Study	Reason for exclusion
Williams 1977	No relevant data, only "Candida-free days"

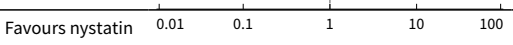
DATA AND ANALYSES

Comparison 1. Nystatin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Colonisation	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.65, 1.13]

Analysis 1.1. Comparison 1 Nystatin versus placebo, Outcome 1 Colonisation.

Study or subgroup	Nystatin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Buchanan 1985	24/39	27/39		45.62%	0.89[0.64,1.23]
Epstein 1992	13/50	11/36		21.61%	0.85[0.43,1.68]
Savino 1994	16/75	19/72		32.76%	0.81[0.45,1.45]
Total (95% CI)	**164**	**147**		**100%**	**0.85[0.65,1.13]**
Total events: 53 (Nystatin), 57 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=2(P=0.95); I^2=0%					
Test for overall effect: Z=1.1(P=0.27)					



Comparison 2. Fluconazole versus nystatin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Colonisation	9	947	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.36, 0.68]
2 Fungal invasion	6	617	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.17, 0.93]
3 Death	6	692	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.54, 1.03]

Analysis 2.1. Comparison 2 Fluconazole versus nystatin, Outcome 1 Colonisation.

Study or subgroup	Fluconazole n/N	Nystatin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Egger 1995	11/43	17/46		10.9%	0.69[0.37,1.31]
Ellis 1994	11/42	23/48		11.61%	0.55[0.3,0.98]
Feusner 1994	0/89	7/89		1.18%	0.07[0,1.15]
Flynn 1995	17/72	48/54		14.24%	0.27[0.17,0.41]
Groll 1997	17/25	19/25		15.56%	0.89[0.63,1.27]
Lumbreras 1996	19/76	35/67		13.81%	0.48[0.3,0.75]
Pons 1997	27/68	62/66		16.33%	0.42[0.31,0.57]
Tian 1997	5/40	11/40		7%	0.45[0.17,1.19]
van Delden 1995	8/32	11/25		9.37%	0.57[0.27,1.2]
Total (95% CI)	**487**	**460**		**100%**	**0.5[0.36,0.68]**
Total events: 115 (Fluconazole), 233 (Nystatin)					
Heterogeneity: Tau^2=0.14; Chi^2=24.81, df=8(P=0); I^2=67.75%					
Test for overall effect: Z=4.28(P<0.0001)					

Favours fluconazole — Favours nystatin

Analysis 2.2. Comparison 2 Fluconazole versus nystatin, Outcome 2 Fungal invasion.

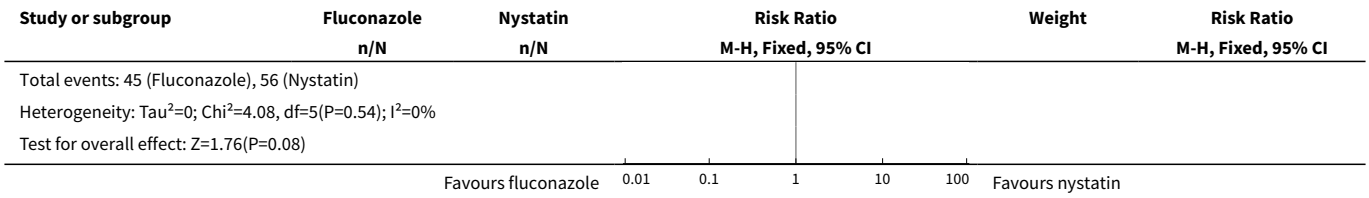
Study or subgroup	Fluconazole n/N	Nystatin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Egger 1995	1/43	2/46		10.86%	0.53[0.05,5.69]
Ellis 1994	2/42	7/48		36.72%	0.33[0.07,1.49]
Feusner 1994	0/89	3/89		19.67%	0.14[0.01,2.73]
Groll 1997	1/25	0/25		2.81%	3[0.13,70.3]
Lumbreras 1996	1/76	4/67		23.9%	0.22[0.03,1.92]
van Delden 1995	1/36	1/31		6.04%	0.86[0.06,13.2]
Total (95% CI)	**311**	**306**		**100%**	**0.4[0.17,0.93]**
Total events: 6 (Fluconazole), 17 (Nystatin)					
Heterogeneity: Tau^2=0; Chi^2=2.76, df=5(P=0.74); I^2=0%					
Test for overall effect: Z=2.12(P=0.03)					

Favours fluconazole — Favours nystatin

Analysis 2.3. Comparison 2 Fluconazole versus nystatin, Outcome 3 Death.

Study or subgroup	Fluconazole n/N	Nystatin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ellis 1994	8/42	17/48		27.03%	0.54[0.26,1.12]
Flynn 1995	2/94	0/88		0.88%	4.68[0.23,96.23]
Groll 1997	1/25	0/25		0.85%	3[0.13,70.3]
Lumbreras 1996	10/76	9/67		16.3%	0.98[0.42,2.27]
van Delden 1995	18/35	19/29		35.4%	0.78[0.52,1.19]
Young 1999	6/85	11/78		19.54%	0.5[0.19,1.29]
Total (95% CI)	**357**	**335**		**100%**	**0.75[0.54,1.03]**

Favours fluconazole — Favours nystatin



ADDITIONAL TABLES

Table 1. Harms

Trial	Experimental drug	Control	Number of patients	Harms
Epstein 1992	nystatin	saline	50 versus 36	No data
Savino 1994	nystatin	none	75 versus 72	No data
Buchanan 1985	nystatin	fluconazole	39 versus 39	No data
Egger 1995	nystatin	fluconazole	46 versus 43	Treatment discontinuations: 3 (poor tolerance and severe vomiting) versus 1 (rising liver enzymes). Oral administration of nystatin was difficult in patients receiving therapy for more than 2 weeks
Ellis 1994	nystatin	fluconazole	48 versus 42	Treatment discontinuations: none for more than one day at the time; Nausea: 3 versus 0; Severe calf cramps: 0 versus 1. Several patients had difficulties in sucking the trouches due to mucositis. More patients on fluconazole had minor bilirubin changes; mean increases in liver enzymes similar in the two groups
Feusner 1994	nystatin	fluconazole	178 total	Treatment discontinuations: 0 versus 5 (1 seizure, 2 vomiting, 1 nausea, 1 rash); Other harms: 21 versus 25 (mostly gastrointestinal)
Flynn 1995	nystatin	fluconazole	88 versus 94	Treatment discontinuations: 0 versus 2 (gastrointestinal effects); "Clinical side effects thought to be related to treatment": 3 versus 7 (mostly gastrointestinal); Liver function test abnormalities: 7% versus 8%
Groll 1997	nystatin	fluconazole	25 versus 25	Treatment discontinuations: none; Nausea and gastrointestinal discomfort: 0 versus 3; Pruritus: 0 versus 1; Elevated liver enzymes: 3 versus 7
Lumbreras 1996	nystatin	fluconazole	67 versus 76	Treatment discontinuations: 0 versus 1 (confusion); Adverse events ascribed to drugs: 25% versus 33%; Mild gastrointestinal symptoms: 19% versus 9%; Acute renal failure: 12% versus 13%; Liver enzymes: "no differences" (no data)
Pons 1997	nystatin	fluconazole	84 versus 83	Treatment discontinuations: 2 versus 3 (adverse effects or abnormal laboratory values, including 1 vomiting versus 1 nausea and 1 liver enzymes increase); Other harms: no data
Tian 1997	nystatin	fluconazole	40 versus 40	No data

Table 1. Harms *(Continued)*

van Delden 1995	nystatin	fluconazole	33 versus 36	Treatment discontinuations: 4 (1 mucositis, 1 rash, 1 vomiting) versus 0; Rash: 3 versus 6
Young 1999	nystatin	fluconazole	78 versus 86	Treatment discontinuations: 11 versus 6 (reasons not specified, most common were gastrointestinal adverse effects); Liver enzyme increase: 19 versus 7; Other harms: similar (extensive table on harms)
Powles 1999	nystatin	amphotericin B	16 versus 15	Treatment discontinuations: 6 versus 3; Infusion related toxicity: 15 versus 10; Renal impairment: 0 vs 3; Liver dysfunction: 0 versus 2

APPENDICES

Appendix 1. PubMed search strategy

#1: random* OR control* OR blind*
#2: nystatin OR amphotericin OR fluconazol* OR itraconazol* OR ketoconazol* OR miconazol* OR voriconazol*
#3: bone-marrow OR cancer* OR fungemia OR hematologic* OR malignan* OR neoplas* OR neutropeni* OR granulocytopeni* OR leukemi* OR lymphom*
#4: #1 AND #2 AND #3.

WHAT'S NEW

Date	Event	Description
8 March 2017	Review declared as stable	Intervention no longer in general use.

HISTORY

Review first published: Issue 2, 2000

Date	Event	Description
7 July 2014	New citation required but conclusions have not changed	No new trials identified for inclusion
7 July 2014	New search has been performed	Literature searches updated
14 September 2011	New search has been performed	Review updated with new search details. No new studies were identified for inclusion.
18 July 2011	Amended	Searches re-run July 2011.
5 February 2008	New search has been performed	Minor update
5 November 2007	New search has been performed	New studies found and included or excluded:One new outcome added (harms), one excluded trial added (Epstein)
29 July 2002	New search has been performed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HKJ wrote the draft meta-analysis protocol, HKJ and PG contributed equally to selection of trials, data extraction and writing of the manuscript. Guarantors: both authors.

DECLARATIONS OF INTEREST

Peter C Gøtzsche - nothing to declare
Helle Krogh Johansen - nothing to declare

SOURCES OF SUPPORT

Internal sources

- Rigshospitalet, Denmark.

External sources

- JASCHA-fonden, Denmark.
- Nordic Council of Ministers, Denmark.
- The Swedish Society of Medicine, Sweden.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was no separate protocol for this review as we were asked by the editors of JAMA to do an additional meta-analysis on nystatin when we published our review on fluconazole (Johansen 1999); we therefore based the current review as part of the protocol for the fluconazole review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; *Immunocompromised Host; Amphotericin B [therapeutic use]; Antifungal Agents [*therapeutic use]; Candidiasis [drug therapy]; Fluconazole [therapeutic use]; Liposomes; Mycoses [drug therapy] [mortality] [*prevention & control]; Nystatin [*therapeutic use]; Opportunistic Infections [drug therapy] [mortality] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans