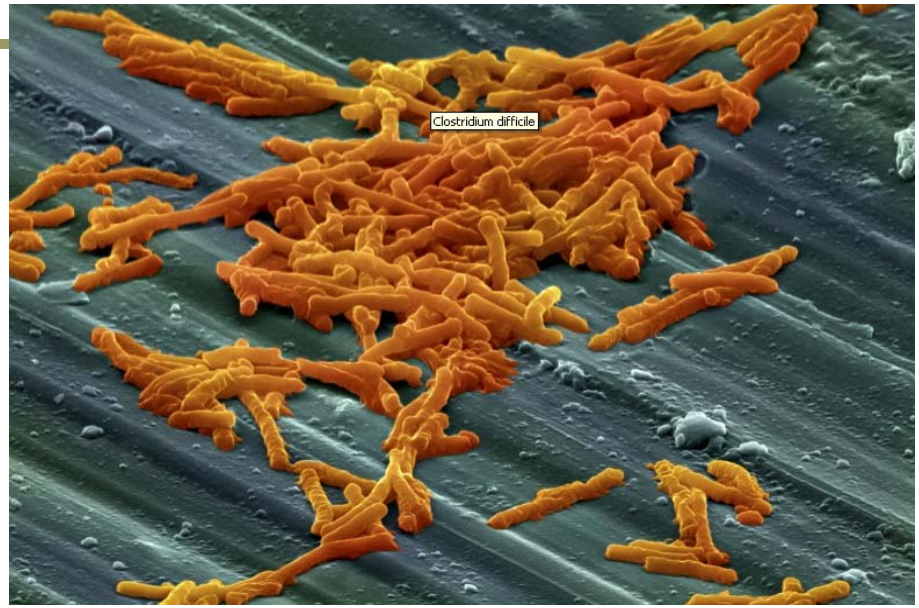


Infection control methods for cancer patients undergoing treatment:

Infection control measures for prevention of fungal infections in neutropenic patients

Petra Gastmeier

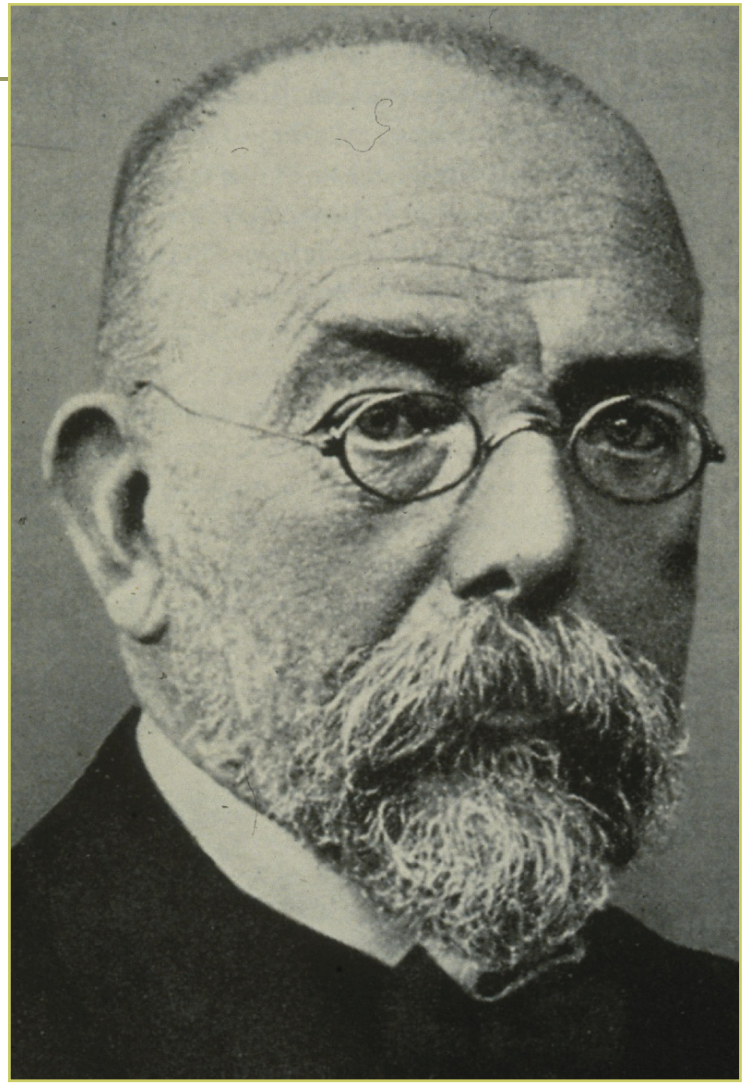
CHARITÉ

2010: 300 years Charité hospital Berlin

- 3200 beds
- largest university hospital in Germany
- 3 haematology/ oncology departments

CHARITÉ

2010: 125 years Institute for Hygiene



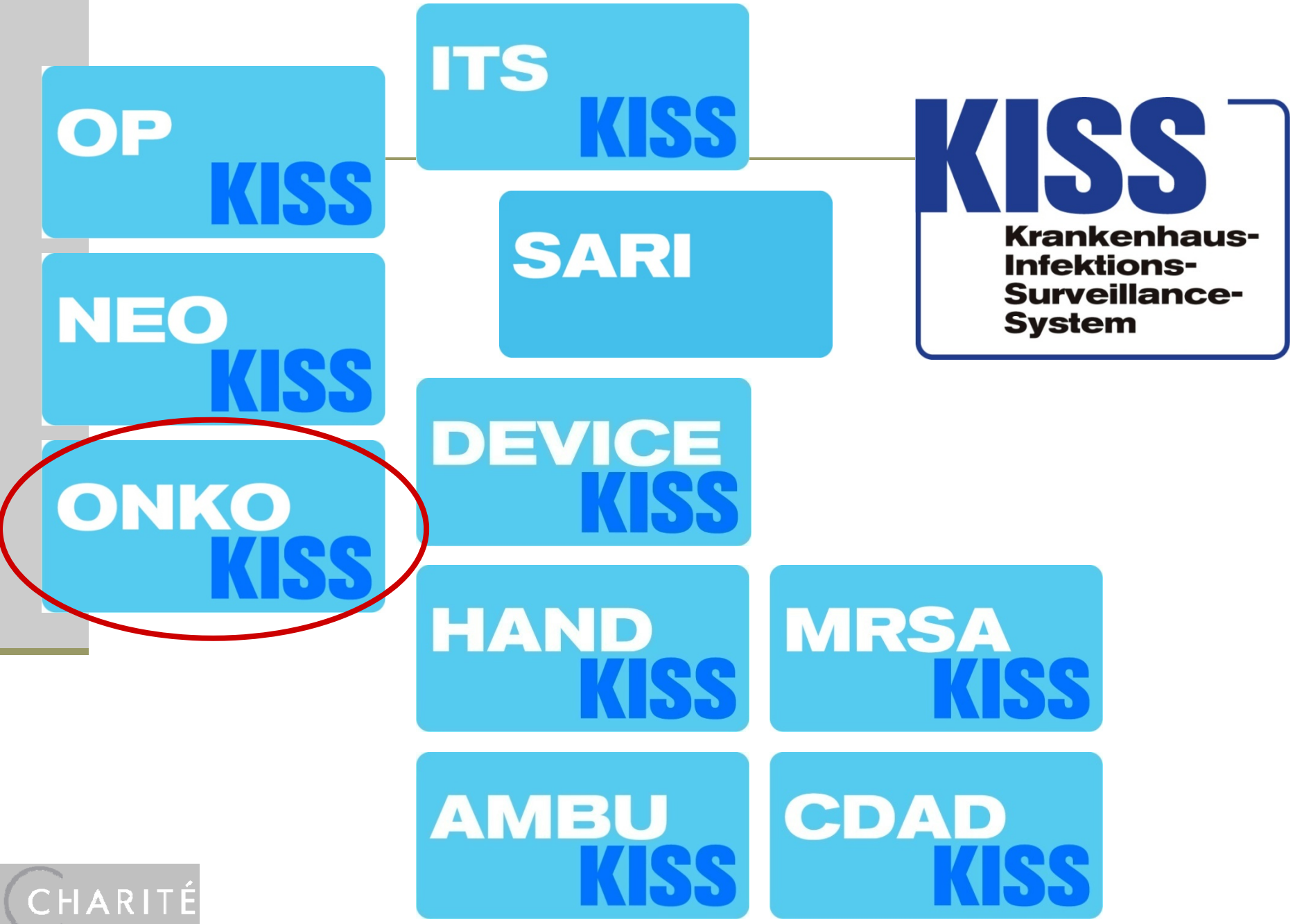
CHARITÉ

Charité University Hospital Berlin

Institute of Hygiene =

National Reference Center for Surveillance of nosocomial infections

supported by the German Ministry of Health


OP KISS
NEO KISS
ONKO KISS
ITS KISS
SARI
DEVICE KISS
HAND KISS
MRSA KISS
AMBU KISS
CDAD KISS
KISS
Krankenhaus-
Infektions-
Surveillance-
System

Endpoints

$$\text{Primary BSI rate} = \frac{\text{Primary BSI cases}}{\text{Neutropenia days}} \times 1000$$

$$\text{Pneumonia rate} = \frac{\text{Pneumonia cases}}{\text{Neutropenia days}} \times 1000$$

- Autologous transplant patients, 25 departments
- Allogenic transplant patients, 19 departments
- Participation is voluntary, confidential data feedback
- www.nrz-hygiene.de

Distribution of infection rates 2006-2010

Autologous transplant patients

Infection rate	Patients	Infections	Median	75th percentile
Primary BSI / 1000 neutroenic days	2658	373	14.3	19.0
Pneumonia cases / 1000 neutropenic days	2658	99	2.4	5.2

Allogenic transplant patients

Infection rate	Patients	Infections	Median	75th percentile
Primary BSI / 1000 neutroenic days	3719	619	19.8	23.0
Pneumonia cases / 1000 neutropenic days	3719	333	8.7	18.2

ONKO-KISS – Krankenhaus-Infektions-Surveillance-System auf Knochenmark- und Blutstammzell-Transplantationsabteilungen
Berechnungszeitraum: Juli 2003 bis Juni 2008

Referenzdaten für Knochenmark- und Blutstammzell- Transplantationsabteilungen

Allogene Transplantationen

Anzahl Kliniken: 19
Anzahl Abteilungen: 20
Anzahl Patienten: 3.189
Anzahl Neutropenietage: 60.665
Anzahl Patienten mit NI: 778

Verteilung Neutropeniedauer

Neutropeniedauer			
Gepoolt	25%-Quantil	50%-Quantil	75%-Quantil
19,0	17,8	18,5	20,3

Inzidenzdichten über alle Patienten mit allogener Transplantation

Art der Infektion	Anzahl Infektionen	Inzidenzdichte			
		Gepoolt	25%-Quantil	50%-Quantil	75%-Quantil
Sepsis	525	8,7	7,8	9,9	12,2
Pneumonie	363	6,0	4,9	7,2	10,8

Inzidenzdichte = Anzahl Infektionen / Anzahl Neutropenie-Tage x 1000

www.nrz-hygiene.de

ONKO KISS

BSI cases

Autologous tranplant patients

Incidence: 8/2658 = 0,3 %

Allogenic tranplant patients

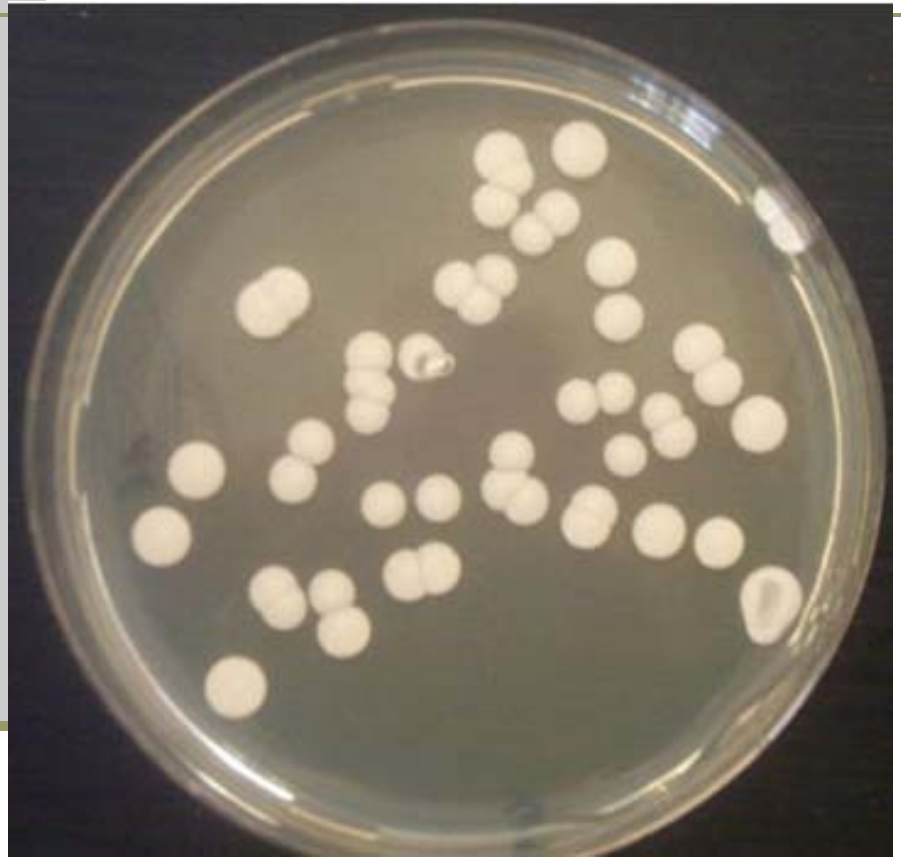
Incidence:31/3719 = 0.8 %

Pathogen	n
C.krusei	8
C.albicans	5
C. tropicalis	3
C. glabrata	1
C. guiellermondi	1
C. parapsilosis	1
Candida spp.	15

Only during neutropenic period !

CHARITÉ

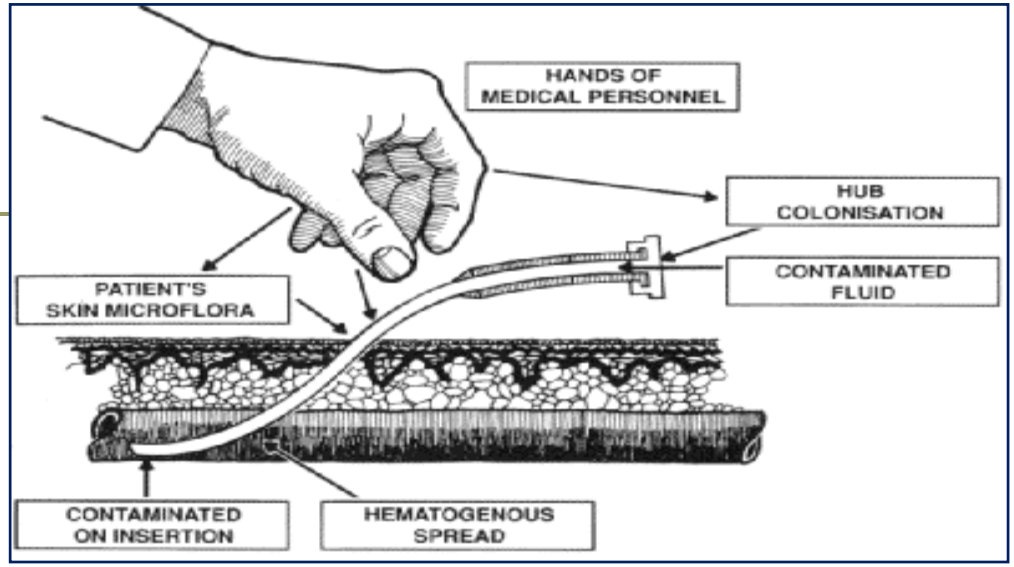
Candida spp.



Often endogenous infections

selection following broad spectrum antibiotic usage

but also transmission via hands of HCW



In general the same prevention measures as used for bacterial infections

Only during neutropenic period !

Pneumonia cases

Autologous transplant patients

Incidence : 0/2658 = 0 %

Allogenic transplant patients

Incidenc: 11/3719 = 0.3 %

Pathogen	n
A. fumigatus	1
A. flavus	1
Aspergillus spp.	8
Absidia spp	1

Molds

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ONKO KISS

1. Surveillance

Hospitals caring for neutropenic patients should establish ongoing surveillance of IFI to detect increases in incidence

Aspergillosis cases

It is necessary to perform a regular review of microbiological and pathology reports suggestive of infection.

1. Surveillance

EORTC/MSG defined 3 levels of diagnostic probabilities

„proven"

„probable"

„possible"

These criteria were designed for clinical research, but can also be applied to infection control surveillance.

De Pauw B et al. CID 2008; 46:1813-21

1. Surveillance

- it is not possible to reliable distinguish community-acquired from nosocomial cases
- arbitrary cut-off of 7 days has been used by some experts as an incubation period
- also nosocomial when 14 days post discharge

Partridge-Hinckley K et al. Mycopathologia 2009; 168: 329-37

1. Surveillance

DENOMINATORs:

A. Surveillance for the hematology/oncology department
   - per number of patients with neutropenia/ at least 10 days of neutropenia
   - all patient days

   - stratified according to type of therapy

B. Surveillance for the whole hospital
   - per 100 patients/ - per 1000 patient days

Example: Surveillance

Year	Number of cases	Patient days	Incidence density (per 100 000 patient days)
2003	32	391 445	24
2004	16	407 007	15
2005	15	407 644	6
2006	7	415 980	5
2007	11	431.954	4

Graf K et al. BMC Infect Dis; in press

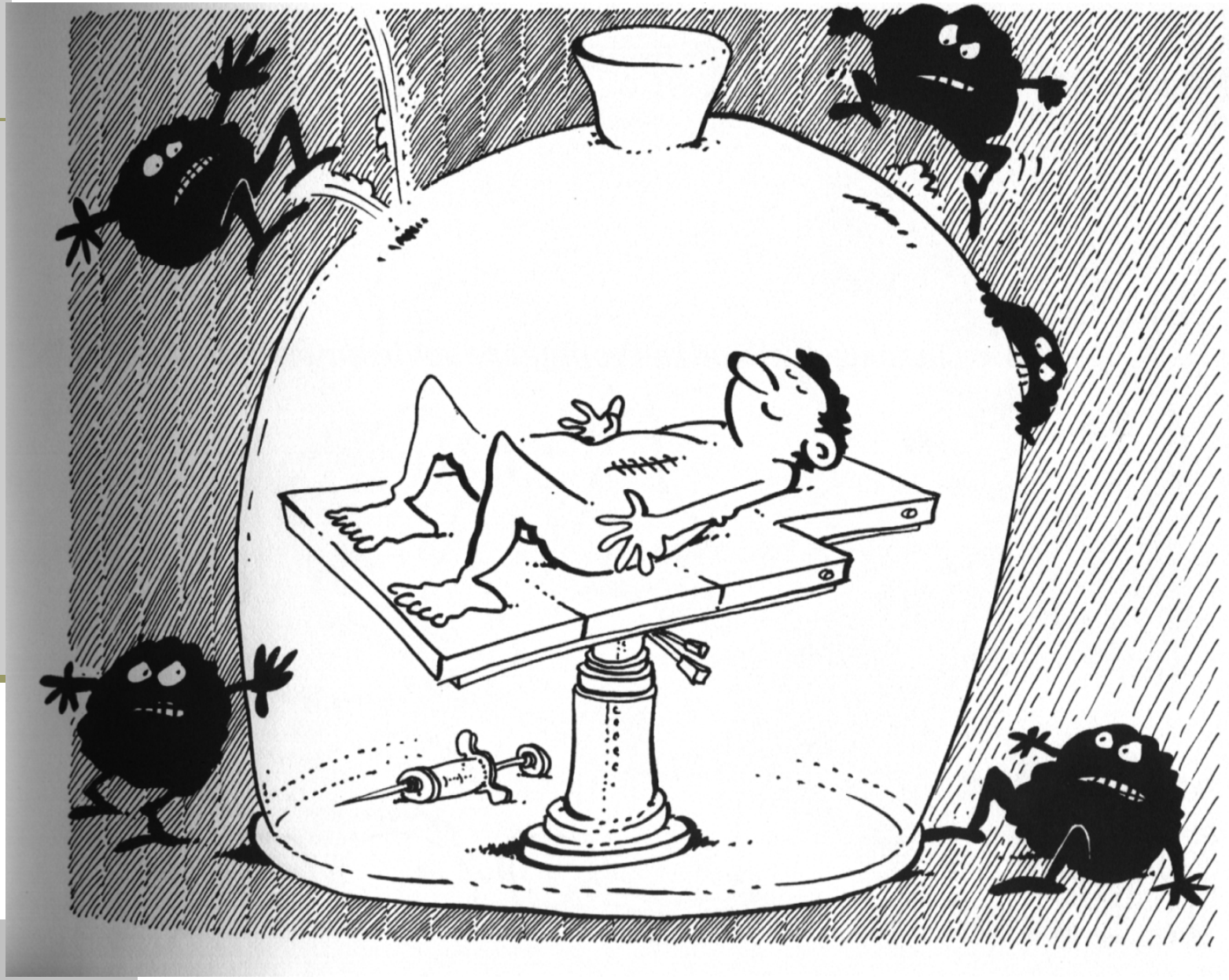
Example: Surveillance

proven	**56**
probable	**25**
possible	133

37	Solid organ transplantation
8	Bone marrow transplantation
10	Malignant tumors
26	Chronical organ diseases

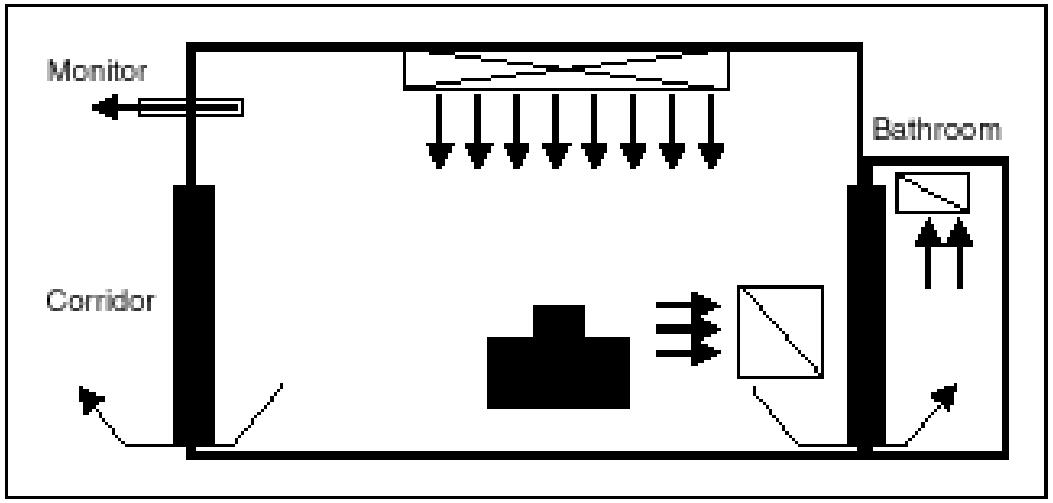
Graf K et al. BMC Infect Dis in press

2. Protective environment



2. Protective environment

FIGURE 1. Example of positive-pressure room control for protection from airborne environmental microbes*†



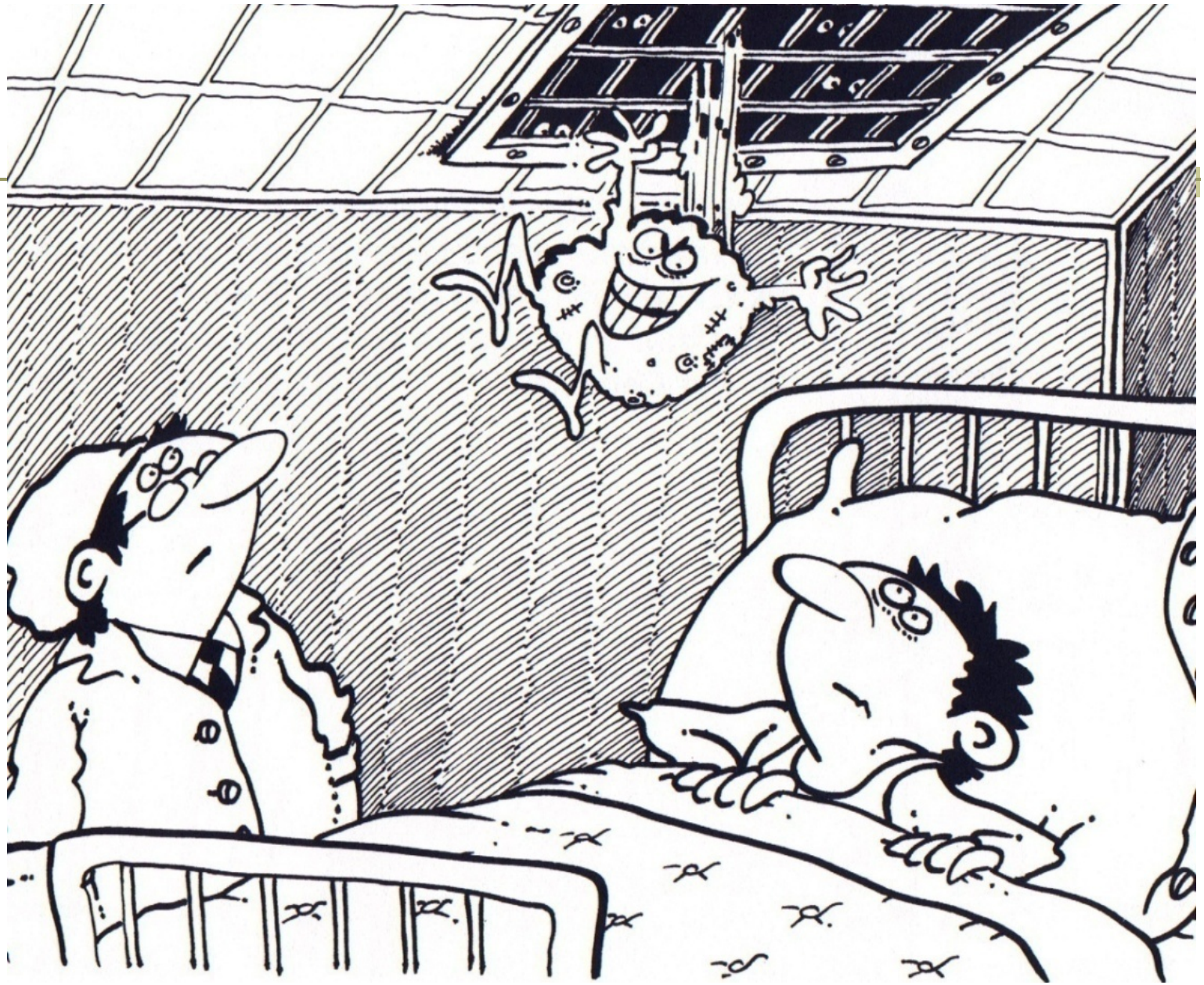
Source: Adapted from Heating/Piping/Air Conditioning (HPAC) Engineering, October 2000, Penton Media, Inc.
Note: Stacked black boxes represent patient's bed. Long open box with cross-hatch represents supply air. Open boxes with single, diagonal slashes represent air exhaust registers. Arrows indicate directions of airflow.

- Positive airflow relative to the corridor
- high number of air changes per hour (> 12 ACH)
- Minimal leakage of air into the room

2. Protective environment

Central or point-of-use high-efficacy particulate air (HEPA) filters with 99.97 % efficacy for removing particles 0.3 µm or larger

Aspergillus conidia
(2.5-3.0 µm diameter)



CHARITÉ

2. Protective environment

Filter efficiency

Filters	Efficiency	(%)
1st	Low	20-40 %
2nd	Medium	90 %
3rd = HEPA*	High	99.97 % for removing particles >0.3 µm in diameter.

HEPA = high-efficiency particulate air

The evidence for HEPA filtration to prevent IFI: Our review

MAJOR ARTICLE

The Influence of High-Efficiency Particulate Air Filtration on Mortality and Fungal Infection among Highly Immunosuppressed Patients: A Systematic Review

Tim Eckmanns,[1] Henning Rüden,[1] and Petra Gastmeier[2]

[1]Institute of Hygiene and Environmental Medicine, Charité–University Medicine Berlin, Berlin, and [2]Institute of Microbiology and Hospital Hygiene, Medical University Hanover, Hanover, Germany

Eckmanns et al. JID 2006; 193:1408–18

CHARITÉ

Method

- 923 articles screened
- Two groups of studies: RCTs and non-RCTs (16 trails included; 8+8)
- Two endpoints:
  mortality (9)
  and fungal infection rate (10)

Table 3. Results of meta-analyses of studies with death as the outcome.

Authors, year of publication [reference]	Patients in rooms with HEPA/LAF ventilation, no.		Patients in rooms with no ventilation system, no.		Total patients, no.	RR (95% CI)	Mortality rate, %		
	Who died	Who survived	Who died	Who survived			With HEPA/LAF ventilation	Without ventilation	Overall
RCTs with death as the outcome									
Yates et al., 1973 [26]	11	24	17	35	87	0.96 (0.51–1.78)	31	33	32
Levine et al., 1973 [27]	1	21	9	29	60	0.19 (0.03–1.42)	5	24	17
Buckner et al., 1978 [24]	23	6	25	2	56	0.86 (0.69–1.06)	79	93	86
Storb et al., 1983 [25]	5	34	28	63	130	0.42 (0.17–1.00)	13	31	25
Petersen et al., 1987 [29]	13	36	12	38	99	1.11 (0.56–2.18)	27	24	25
Petersen et al., 1988 [28]	13	128	15	186	342	1.24 (0.61–2.51)	9	7	8
All	66	249	106	353	774	0.86[a] (0.65–1.14)	21	23	22
Non-RCTs with death as the outcome									
Rodriguez et al., 1978 [24]	39	24	69	13	145	0.74 (0.59–0.91)	62	84	74
Schmeiser et al., 1988 [30]	1	25	0	15	41	1.78 (0.08–41.1)	4	0	2
Gamillscheg et al., 1991 [31]	16	9	11	9	45	1.16 (0.71–1.91)	64	55	60
All	56	58	80	37	231	0.87[a] (0.60–1.25)	49	68	59

NOTE. CI, confidence interval; HEPA, high-efficiency particulate air; LAF, laminar airflow; non-RCT, nonrandomized controlled trial; RCT, randomized controlled trial; RR, relative risk.

[a] Pooled RR determined by the DerSimonian and Laird method.

Table 4. Results of meta-analyses of studies with fungal infection as the outcome.

Authors, year of publication [reference]	Patients in rooms with HEPA/LAF ventilation, no.		Patients in rooms with no ventilation system, no.		Total patients, no.	RR (95% CI)	Fungal infection rate, %		
	With fungal infection	Without fungal infection	With fungal infection	Without fungal infection			With HEPA/LAF ventilation	Without ventilation	Overall
RCTs with fungal infection as the outcome									
Levine et al., 1973 [27]	0	22	3	35	60	0.24 (0.013–4.48)	0	8	5
Schimff et al., 1975 [21]	0	24	1	18	43	0.27 (0.011–6.20)	0	5	2
Buckner et al., 1978 [24]	0	46	3	41	90	0.14 (0.0073–2.57)	0	7	3
Lohner et al., 1979 [32]	5	19	2	19	45	2.19 (0.47–10.1)	21	10	16
All	5	111	9	113	238	0.57[a] (0.13–2.53)	4	7	6
Non-RCTs with fungal infection as the outcome									
Rodriguez et al., 1978 [23]	3	60	9	73	145	0.43 (0.12–1.54)	5	11	8
Navari et al., 1984 [33]	0	36	1	30	67	0.29 (0.012–6.83)	0	3	1
Rhame et al., 1984 [34]	9	158	12	55	234	0.30 (0.13–0.68)	5	18	9
Sherertz et al., 1987 [35]	0	39	14	74	127	0.077 (0.0047–1.25)	0	16	11
Withington et al., 1998 [36]	0	51	1	63	115	0.41 (0.017–10.0)	0	2	1
Oren et al., 2001 [37]	0	26	13	32	71	0.063 (0.0039–1.02)	0	29	18
All	12	370	50	327	759	0.29[a] (0.15–0.54)	3	13	8

NOTE. CI, confidence interval; HEPA, high-efficiency particulate air; LAF, laminar airflow; non-RCT, nonrandomized controlled trial; RCT, randomized controlled trial; RR, relative risk.

[a] Pooled RR, determined by the DerSimonian and Laird method.

Limitations

- Statistical homogeneity was considerable, huge differences in rates of infection and death
- studies performed over a very long period included (28 years)
- folllow-up periods differed significantly
- Severity and duration of neutropenia?
- 3 studies used decontamination (with oral antibiotics)
- 2 studies used HEPA filtration only, the others in combination with LAF
- no study was blinded

Eckmanns et al. JID 2006; 193:1408–18

MAJOR ARTICLE

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Tim Eckmanns,[1] Henning Rüden,[1] and Petra Gastmeier[2]

[1]Institute of Hygiene and Environmental Medicine, Charité–University Medicine Berlin, Berlin, and [2]Institute of Microbiology and Hospital Hygiene, Medical University Hanover, Hanover, Germany

Conclusion

- Patients with BMT receive some benefit if they are placed in a protected environment
- Nevertheless the evidence is still somewhat ambiguous
- No final conclusion can be drawn from the data available

Eckmanns et al. JID 2006; 193:1408–18

The evidence for HEPA filtration to prevent IFI: A new systematic review

Review

Infection-control interventions for cancer patients after chemotherapy: a systematic review and meta-analysis

Agata Schlesinger, Mical Paul, Anat Gafter-Gvili, Bina Rubinowitch, Leonard Leibovici

To quantify the evidence for infection-control interventions among high-risk cancer patients and haematopoietic stem-cell recipients, we did a systematic review of prospective comparative studies. Protective isolation, including air quality control, prophylactic antibiotics, and barrier isolation (29 studies), brought about a significant reduction in all-cause mortality: risk ratio 0·60 (95% CI 0·50–0·72) at 30 days (number needed to treat [NNT] 20 [95% CI 14–33]) and 0·86 (95% CI 0·81–0·91) at the longest follow-up (up to 3 years; NNT 12 [95% CI 9–20]). Inclusion of prophylactic

Lancet Infect Dis 2009; 9: 97–107
Published Online December 17, 2008
DOI:10.1016/S1473-3099(08)70284-6

Schlesinger et al. Lancet Infect Dis 2009; 9: 97-107

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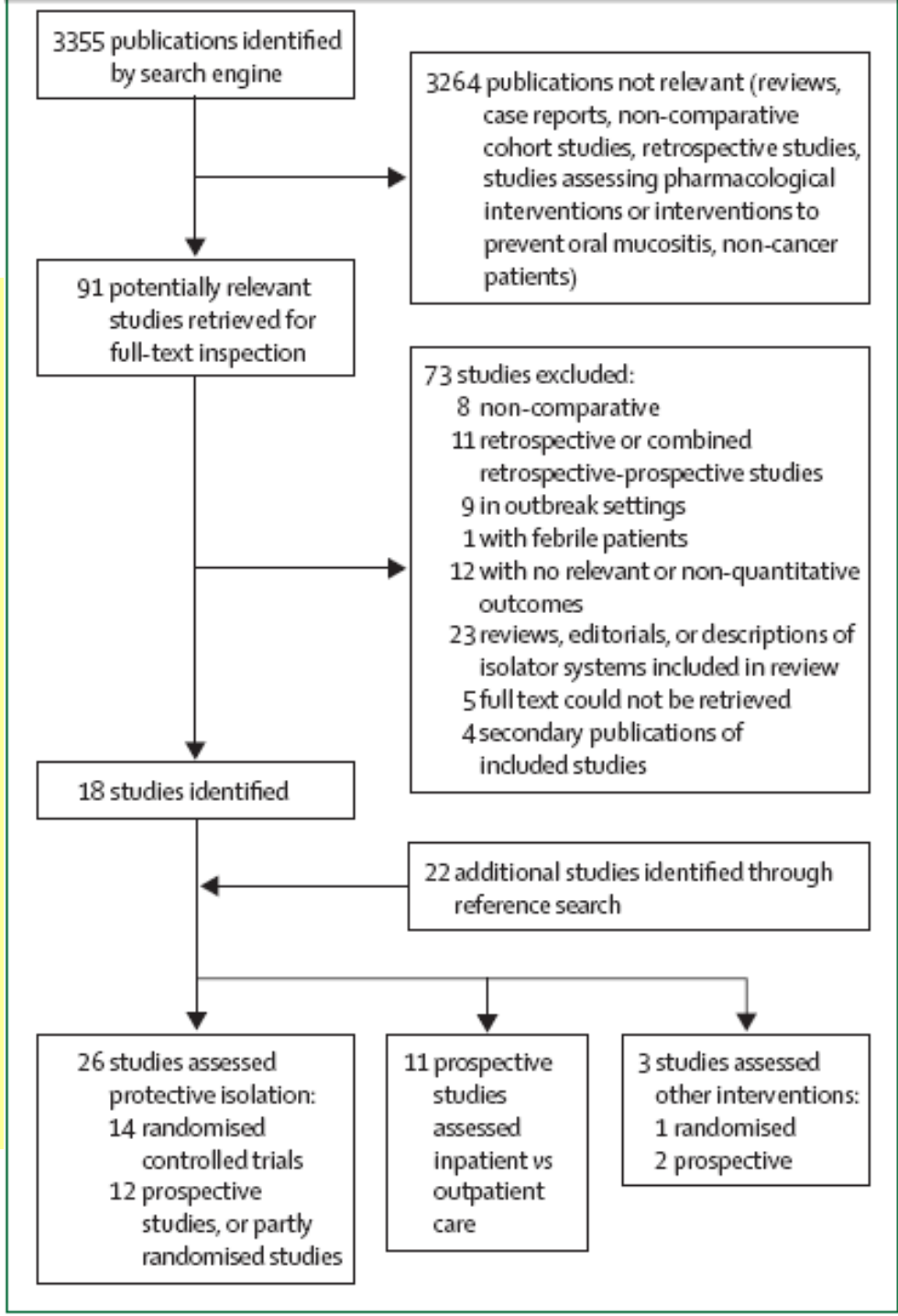
Method

- Broader approach:
  "protective isolation" =
  - air quality control
  - prophylactic antibiotics
  - and barrier isolation

- Also RCTs and non-RCTs included
- mortality at day 30
- mortality at the longest follow-up



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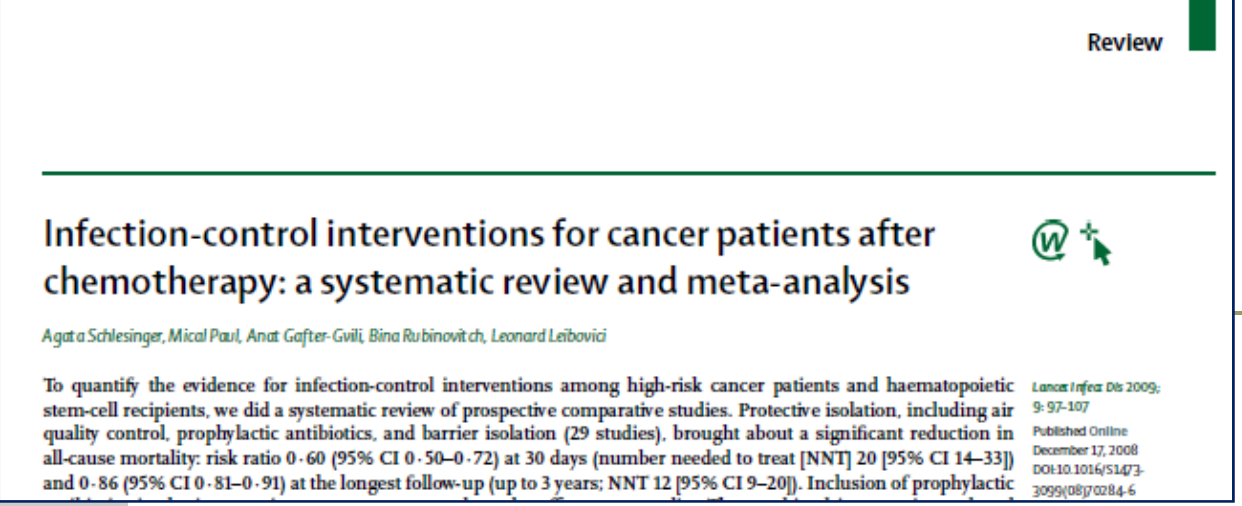

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Lancet Infect Dis 2009; 9: 97-107
Published Online December 17, 2008
DOI:10.1016/S1473-3099(08)70284-6

Conclusion

- "Air quality control, using HEPA filtration with or without other control measures, had only a modest effect on invasive mould infections and survival that did not reach significance.
- Its use should be probably reserved for patients at highest risk for invasive mould infections and for endemic or outbreak settings.

Schlesinger et al. Lancet Infect Dis 2009; 9: 97-107

What patients should be hospitalized in protected rooms?

Patients

- with allogenic transplants of haematopoietic stem cells or
- with severe neutropenia (< 100 cells/mm_3) of more than 1 week‘s duration

Ruiz-Camps I et al. Clin Micro Infect 2011; 17 (suppl 2), 1-24

HEPA FILTRATION

WITH OR WITHOUT

LAF (= laminar airflow)

Laminar airflow (LAF)

PRO:
- involves much greater air changes
- helps to minimize opportunities for microorganism proliferation

CON:
- much higher expense
- inconvenience to the patient due to noise and draughts

Positive-pressure isolation and the prevention of invasive aspergillosis. What is the evidence?

- On balance, the additional expense and inconvenience of LAF does not appear to be justified.

H. Humphreys, J Hosp Infect 2004; 56: 93-100

A survey in 180 centers 1999
(European Group for Bone and Marrow Transplantation; EBMT)

	HEPA	LAF
Allogenic HSCT	61 %	42 %
Autologous HSCT	47 %	24 %

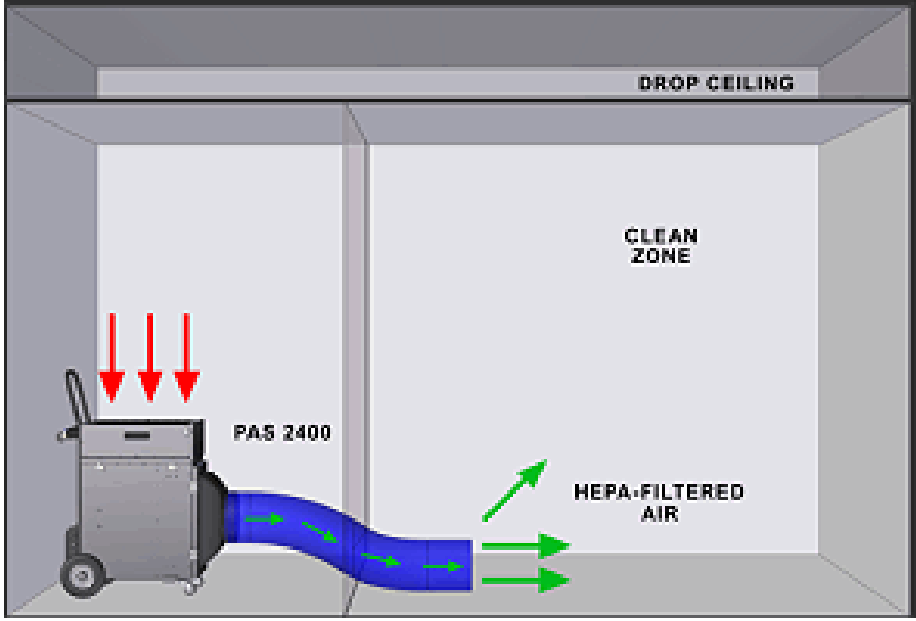
Kruger WH et al. *J Hematother Stem Cell Res 2001; 10: 895–903.*

A survey in 30 centers in Germany 2005
(ONKO-KISS group)

	HEPA	LAF
Allogenic HSCT	83 %	54 %
Autologous HSCT	53 %	28 %

Conrad et al. ECCMID 2006, Nice

Fixed and portable HEPA filters



- Portable HEPA units are available that can filter air at a rate of 300–800 ft3/min.
- Portable HEPA filters are used temporarily in rooms with no general ventilation or to augment systems that cannot provide adequate airflow

- They should achieve the equivalent of $\geq$12 ACH.
  (An average room has approximately 1,600 ft3 of airspace.)

3. Cleaning and disinfection measures for protected areas

The crucial point is designated and trained staff for cleaning!

The use of cleaning tools that may create dust or aerosols is absolutely contraindicated.

Almost all substances used for surface disinfection are able to eliminate fungi and fungal spores

4. Can patients at risk be moved around the hospital?

original article

Annals of Oncology 20: 1560–1564, 2009
doi:10.1093/annonc/mdp034
Published online 18 May 2009

A prospective, randomised study on the use of well-fitting masks for prevention of invasive aspergillosis in high-risk patients

G. Maschmeyer[1]*, S. Neuburger[2], L. Fritz[1], A. Böhme[3], O. Penack[4], R. Schwerdtfeger[5], D. Buchheidt[6] & W.-D. Ludwig[7] on behalf of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology

[1]*Department of Haematology and Oncology, Ernst-von-Bergmann Clinic, Potsdam;* [2]*Department of Haematology and Oncology, Charité University Medical School, Campus Virchow-Klinikum, Berlin;* [3]*Department of Internal Medicine II, Johann-Wolfgang-Goethe-University Medical Centre, Frankfurt am Main;* [4]*Department of Haematology and Oncology, Charité University Medical School, Campus Benjamin Franklin, Berlin;* [5]*Centre for Bone Marrow and Stem Cell Transplantation, German Diagnostic Clinic DKD, Wiesbaden;* [6]*Department of Internal Medicine III, University Medical School Mannheim, Ruprecht-Karls-University of Heidelberg, Mannheim and* [7]*Department of Haematology, Oncology and Tumour Immunology, Robert Roessle-Clinic, Helios Clinic Berlin-Buch, Charité University Medical School, Berlin, Germany*

Received 22 July 2008; revised 22 October 2008; accepted 26 January 2009

Maschmeyer et al. Ann Oncology 2009; 20: 1560-64

- Adults undergoing chemotherapy for acute leukaemia or allogeneic haemato-poietic stem-cell transplantation (aHSCT).

41 patients (masks)
39 patients control group

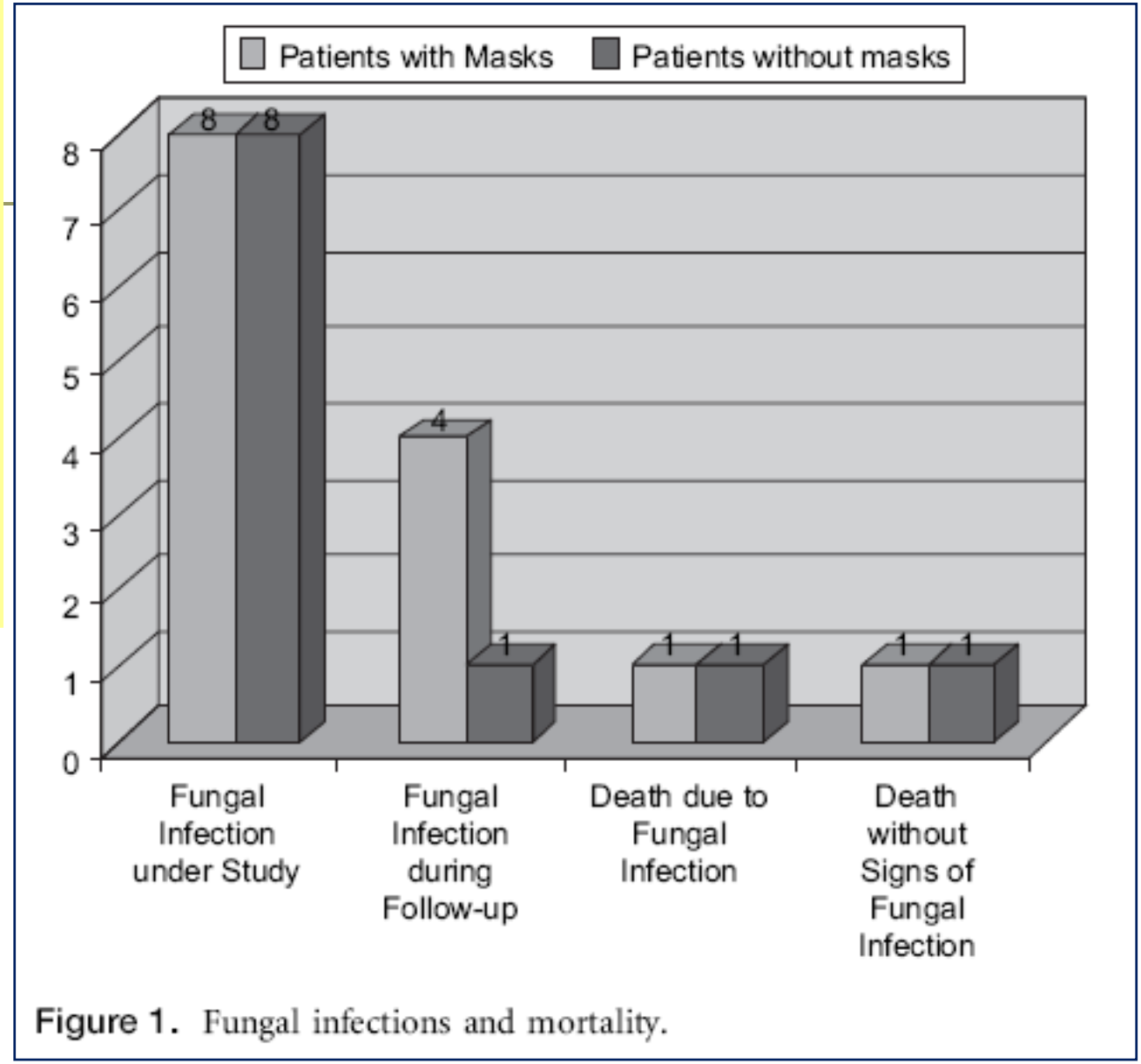


Figure 1. Fungal infections and mortality.

Maschmeyer et al.
Ann Oncology 2009;
20: 1560-64

This first randomised study on the use of well-fitting masks failed to show a reduction of invasive fungal infections.

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5. Routine environmental cultures

Only useful in HEPA-filtered rooms to test the system

- once a year,
- occurrence of Aspergillosis cases
- construction work

Conidia count: < 0.1 CFU/m3

5. Routine environmental cultures

Not useful in unfiltered areas;

Significant variation according to
- geographical area
- degree of activity in the area sampled
- temperature
- humidity

Condida count: usually between 10-25 CFU/m3

5. Routine environmental cultures

No fixed rules for sampling

- Various methods and equipment
- Quantitative results

6. Infection control measures during construction projects

Successful control of an outbreak of invasive aspergillosis in a regional haematology unit during hospital construction works☆

C.C. Chang [a], A.C. Cheng [a], B. Devitt [b], A.J. Hughes [a], P. Campbell [b], K. Styles [c], J. Low [c], E. Athan [a,*]

[a] *Department of Infectious Diseases, Geelong Hospital, Geelong, Victoria, Australia*
[b] *Clinical Haematology Unit, Geelong Hospital, Geelong, Victoria, Australia*
[c] *Infection Prevention Unit, Geelong Hospital, Geelong, Victoria, Australia*

Received 19 November 2007; accepted 7 February 2008
Available online 3 April 2008

Outbreak of six cases of nosocomial invasive aspergillosis (IA) in a haematology unit coinciding with major hospital construction works.

Chang et al. J Hosp Infect 2008; 69:33-38

Chang et al. J Hosp Infect 2008; 69:33-38

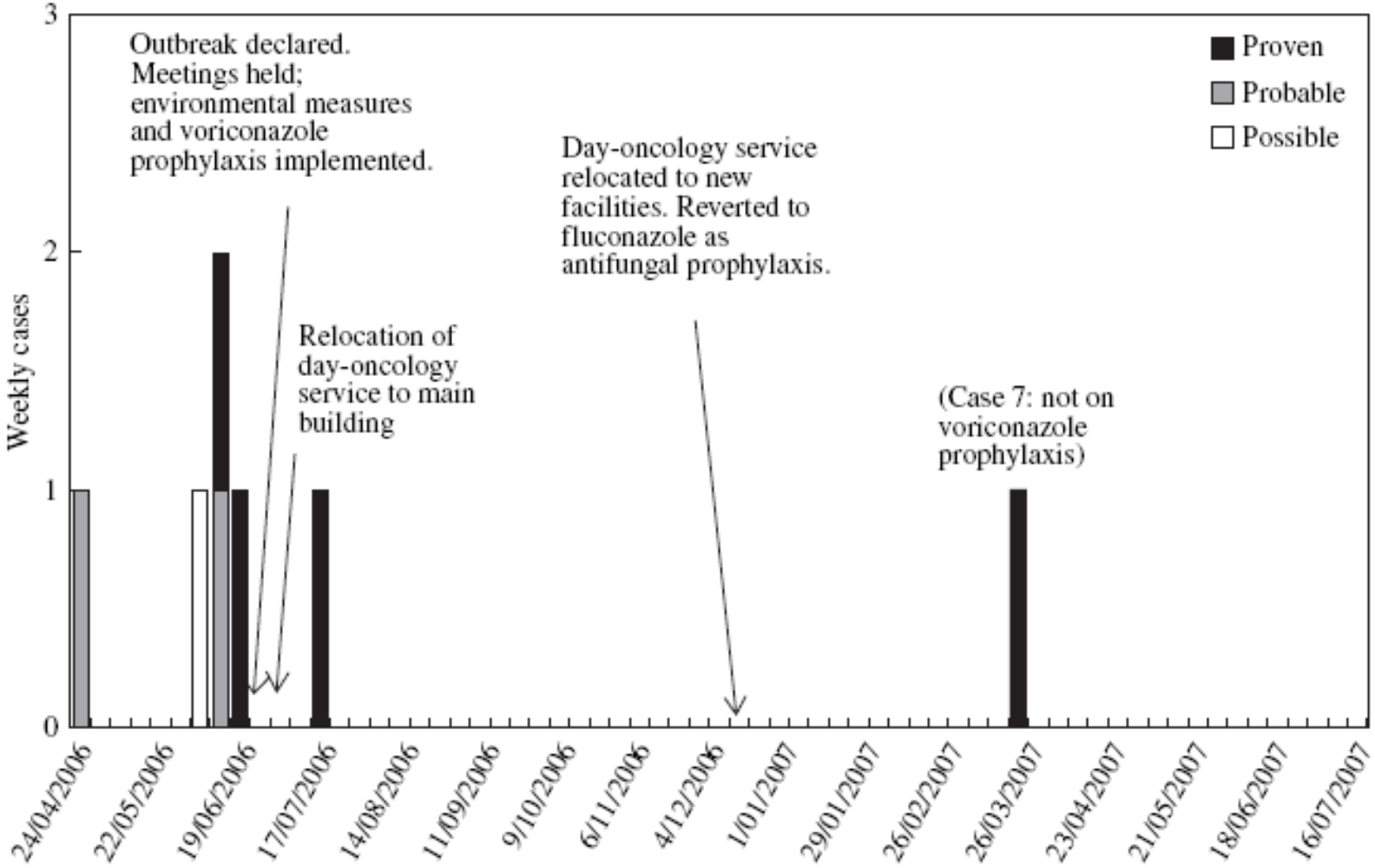

Figure 2 Timeline of invasive aspergillosis outbreak.

Among 18 following high-risk patients only one developed IA.

Journal of Hospital Infection (2006) 63, 246–254

Available online at www.sciencedirect.com

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www.elsevierhealth.com/journals/jhin

REVIEW

Nosocomial aspergillosis in outbreak settings

R-P. Vonberg*, P. Gastmeier

Institute for Medical Microbiology and Hospita

53 outbreaks
involving 458 patients

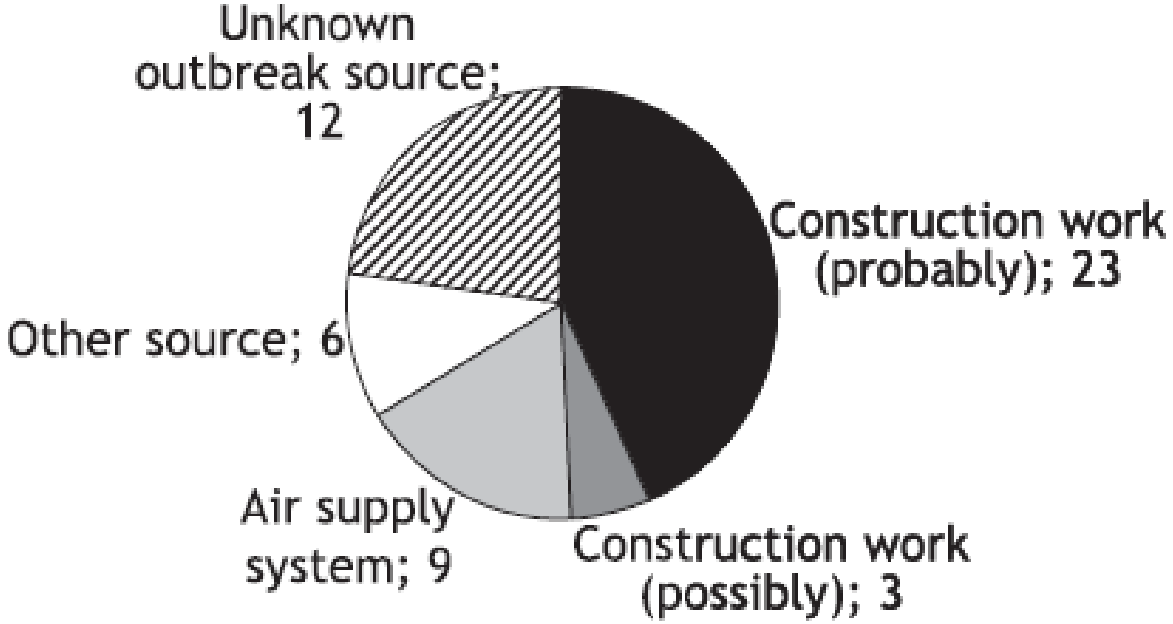

Figure 1 Distribution of sources of nosocomial aspergillus outbreaks.

CHARITÉ

6. Infection control measures during construction projects

- set up a multidisciplinary team that includes infection control staff to coordinate proactive prevention measures to reduce exposure to fungal spores and **monitor adherence**

- provide education to HCW and the construction crew in immunocompromised patient care areas regarding aspergillosis

- dust control measures (dust barriers, safe air handling, negative pressure in construction work zones)

- water damage response plan to prevent fungal growth

- maintain surveillance for asperillosis cases

Alangaden GJ Infect Dis Clin N Am 2011; 25:201-25

Journal of Hospital Infection (2006) 63, 246–254

Available online at www.sciencedirect.com

SCIENCE DIRECT

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www.elsevierhealth.com/journals/jhin

REVIEW

Nosocomial aspergillosis in outbreak settings

R-P. Vonberg*, P. Gastmeier

Institute for Medical Microbiology and Hospital Epidemiology, Medical School Hannover, Germany

Volumetric air sampling performed during the course of epidemiologic investigations in 24 of the outbreaks noted spore counts ranging from 0 to 100 spores per cubic meter

Data from outbreak analyses have shown that it is impossible to provide a threshold below no problems are expected

Poor correlation of Aspergillus ssp. recovered from the environment and species isolated from patients with aspergillosis

Explanations:

- Lack of a clearly defined incubation period for aspergillosis and the relationship to exposure within the hospital environment and subsequent infection
- Methods of air sampling used
- Broad diversity of Aspergillus spp. in the environment and the various methods used for typing of Aspergillus

7. Education

Health care workers must receive specific training on epidemiology and prevention measures to control and prevent infections

8. Guidelines for food

Avoiding fresh fruits and vegetables that cannot be effectively washed.

Unpasteurized dairy products, cheese made from mold cultures, uncooked eggs, meat, fish tofu

Marr et al. Bone Marrow Transplantation 2009; 44:483-87

9. Guidelines for outpatient setting

- Avoiding activities such as gardening, mowing and vacuuming
- Avoid cleaning methods that disperse dust (family members)
- Leftover foods placed in the refrigerator should be discarded after 72 h
- Avoid fresh flowers and potted plants

Partridge-Hinckley K et al. Mycopathologia 2009; 168: 329-37

Empfehlung

Bundesgesundheitsbl 2010 · 53:357–388
DOI 10.1007/s00103-010-1028-9
Online publiziert: 20. März 2010

Kommission für Krankenhaushygiene und Infektionsprävention
beim Robert Koch-Institut (RKI)

Anforderungen an die Hygiene bei der medizinischen Versorgung von immunsupprimierten Patienten

Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention beim Robert Koch-Institut (RKI)

GUIDELINE 10.1111/j.1469-0691.2011.03477.x

Guidelines for the prevention of invasive mould diseases caused by filamentous fungi by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

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Ruiz-Camps et al. Clin Micro Infect 2011; 17 (Supl 2):1-24.