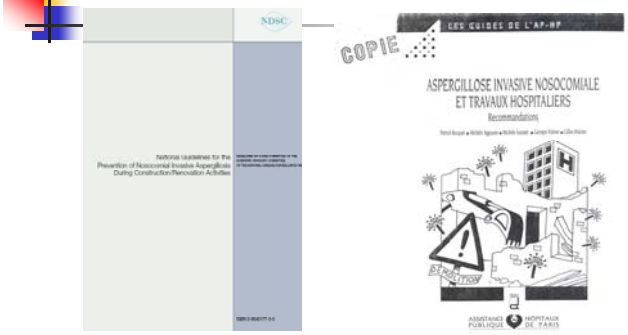
Aspergillus之院內感染管制

衛福部 疾病管制署
中區傳染病防治醫療網
王任賢 指揮官

Guidelines

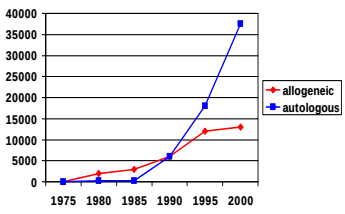
- Healthcare Infection Control Practices Advisory Committee (HICPAC)
  - Guideline for Preventing Healthcare-Associated Pneumonia 2004 CDC
  - Guideline for Environmental Infection Control in Health-Care Facilities, 2003 CDC
    - Air Handling Systems
    - Airborne Infectious Isolation (AII) Rooms
    - Protective Environments (PE)
    - Construction, Renovation, Remediation, Repair & Demolition



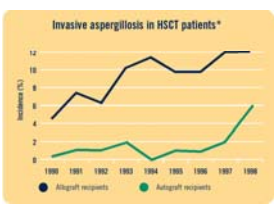
Invasive Aspergillus

- incidence increasing
- commonest cause of infectious death in many transplant units
- commonest cause of death in childhood leukaemia

Increasing incidence?



Source: IBMTR



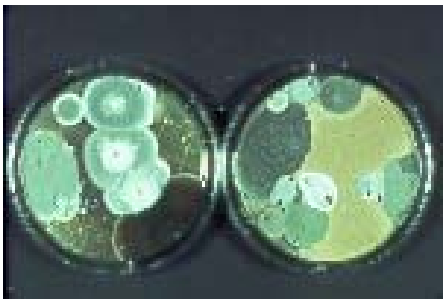
Clinical Infectious Diseases 2002; 34:909

Disease Burden estimates (UK)

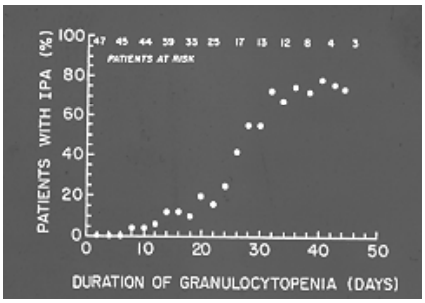
Patient group	Number of patients	Invasive aspergillosis risk estimates	Expected number invasive aspergillosis
AlloBMTx	793	10%	79
Solid organ Tx	2953	1.9%	56
Leukaemia	16269	6%	976
Solid tumour	28955	2%	579
Advanced cancer	131678	1.5%	1975
ICU	210130	0.2%	420
Burns	378	1.9%	7
Renal dialysis	24536	0.02%	5
HIV/AIDS	661	4%	26

Source: HPA Advisory Committee for Fungal Infection and Superficial Parasites:Working group report

Aspergillus in dust

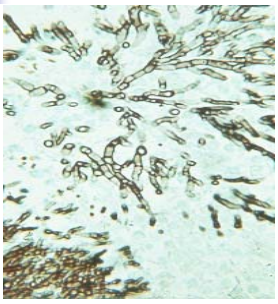


Risk of invasive aspergillosis



Gershon et al

IPA



- Angioinvasion by branching septate hyphae
- lead to infarction of tissues (wedge shaped)
- cavitation of lung
- dissemination

美國1996年Aspergillosis對醫療之衝擊: I

- 共10,190 病例住院，平均住院天數17.3天
- 共造成1970人死亡; 死亡率19.3%
- 造成醫療支出6億3千3百萬美元
- 多出現於肺炎、癌症、血癌、愛滋病之病患身上

Dasbach EJ, Davies GM, Teutsch SM. Clin Infect Dis 2000; 31: 1524-1528

美國1996年Aspergillosis對醫療之衝擊: II

- 若aspergillosis出現在癌症或血癌病人身上時：
  - 增加26個住院日
  - 多增加$115,262美金之額外支出
  - 增加4倍之死亡率

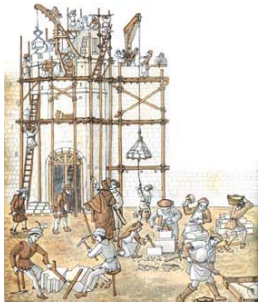
Dasbach EJ, Davies GM, Teutsch SM. Clin Infect Dis 2000; 31: 1524-1528.

醫療機構內侵襲性曲黴菌群聚事件發生之風險因子

- 有增加空氣中曲黴菌孢子數目之活動
- 建築物破壞、重建、修補
- 高風險病人區域出現鳥糞
- 污染的防火建材
- 濕木、石板

Risk factors for aspergillosis

- Neutropenia
- Steroids
- Environmental exposure
  - Building work
  - Compost (堆肥) heaps
  - Marijuana smoking



Problems with air sampling

- Incubation period of IPA unknown
  - Estimates vary from 48 hours -3 months
- Geographical and seasonal variation in spore counts and predominant species
- Variable efficiency of different air samplers
- May not take account of surface contamination
  - Settle plates, contact plates, honey jars

Air sampling

- Patients remain the most efficient "samplers"
- Intermittent periods of spore contamination likely to be missed
- Only useful retrospectively after clusters of disease appear

Protected environment

- HEPA **(for allogeneic HSCT patients only)**
  - 99.97% of all particles >3u diam)
  - >/=12 ACH
  - Pressure differential >2 Pa
  - Directed air flow
  - Sealed rooms
  - Respiratory protection (N95 respirator) if leaving room **only** during periods of building construction
- Standard hygiene barrier precautions
- No flowers, potted plants, carpets
- Vacuums to have HEPA filters

HICPAC guidelines CDC 2004

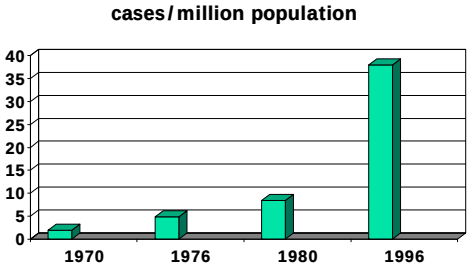
Study (no. of patients)	Patient groups	Results	Comment
Open, randomised (69)	Acute leukaemia	LAF reduced antibiotics reduced incidence of infection and mortality	Difficult to separate effect of ventilation and antibiotics
Open, randomised (37)	Acute leukaemia	No difference in overall infection rate	Isolation may have had adverse consequences on patient care
Open, randomised (38)	Acute leukaemia	Fewer infections, better survival in LAF facilities	LAF room not always available; few fungal infections in either group
Prospective, interventional (113)	Bone marrow transplant recipients	Reduced aspergillus air counts with HEPAs; fewer infections	HEPA not contributory to reduced risk on multivariate analysis
Prospective, interventional (38)	Bone marrow transplant recipients	No aspergillus infection after LAF installed	Suggestive of benefit
Retrospective and prospective after intervention (141)	Leukaemia/bone marrow transplant recipient	Reduced incidence of aspergillosis	Other measures, apart from HEPA likely to have contributed
Prospective, with observational study of air counts (No patients)	Haematology patients	HEPA reduced air counts compared with normal rooms, need LAF during construction	No increase in incidence of infection observed during construction
Retrospective (535)	Solid organ and bone marrow transplant recipient, ICUs	>60% of aspergillosis community-acquired. Removal of carpeting and false ceilings may have led to a decrease in aspergillosis	Lots of variables impact on risk of aspergillosis
Retrospective (91)	Haematology/oncology patients	Installation of HEPA filters ended outbreak	Small number of cases
Retrospective (291)	Chemotherapy patients with neutropenia	Nebulised amphotericin B with HEPA reduced incidence of aspergillosis	Many changes in practice occurred over 18 years

Humphreys H J Hosp Inf 2004 56: 93

Air intake vent

Source: The Aspergillus Website http://www.aspergillus.man.ac.uk

Aspergillus incidence



Source:CDC Atlanta courtesy D Warnock

Despite preventative measures incidence of aspergillosis continues to increase – Why?

- Increasing population at risk
- Improved diagnosis
- Other sources

→ **Changing epidemiology**

Other sources

- Pepper, spices, nuts etc
  - All heavily contaminated with fungal spores
  - No established link with infection proven
- Potted plants
  - Some links with human disease
- Water……..

Fungi in hospital waters

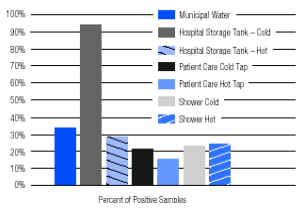
- 90% of specimens contain fungi
- Many species found with wide variation
- Load dependant on water source
  - Surface> underground
  - Tank> mains
  - Associated with biofilms
- Wide seasonal variation

If no contact with ambient air contamination is minimal

aspergillus from hospital water sites

Location	Total samples	Positive samples	Mean cfu*
Intake reservoir	20	17 (85%)	3.1
Untreated water	10	8 (80%)	3.8
Treated water	10	9 (90%)	2.4
Hospital	168	63 (37.5%)[a]	2.0[b]
Main pipe	36	14 (39.8%)[c]	2.1[cd]
Taps	96	47 (49%)[e]	1.9[f]
Showers	36	2 (5.6%)[g]	1.0[h]

Warris et al J Hosp Inf 2001; 47: 143

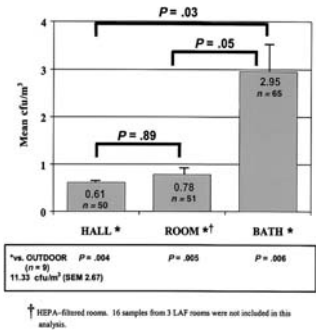


Anaissee et al Clin Infect Dis 2002; 43: 780

Hypothesis

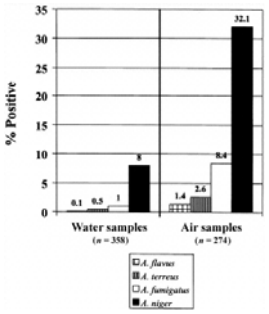
- Moulds can contaminate hospital water supplies
  - No link established between:
    - Ingestion and gastrointestinal disease
    - Contact and cutaneous disease
- Aerosolisation can lead to a source of airborne condia for IPA

Probably.....



Is water a hazard?

- No definite outbreaks linked to water
- Inhalation remains the main portal of entry
- Should neutropenic patients be allowed to shower?



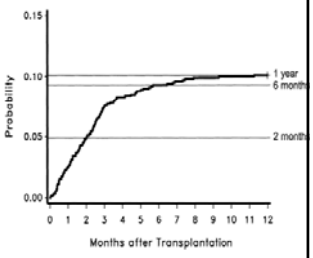
Changing epidemiology

- no longer a neutropenic phenomena
- Majority of infections occur in the late transplant period
  - Associated with chronic GvHD
  - Ongoing immunosuppression
  - Non-myeloablative SCT
  - New immunomodulators

Time to infection (d) Risk of IA

	SCT	SOT
Candidosis	58	107
Aspergillosis	137	172
Zygomycoses	212	280

Source:CDC Atlanta courtesy D Warnock



Marr et al Blood 2000, 100:4358

Protected environments don't work because

- Not all neutropenic patients at same risk
- Many patients not neutropenic
- Many acquire aspergillosis in the community after discharge
- Exposure to sources other than air

What about chemoprophylaxis

Prophylaxis

- Fluconazole
  - No activity against moulds
- Itraconazole
  - Poor tolerability; 30% cannot comply
  - Levels must be monitored and kept >0.5g/L
  - Need to continue 100-180 days or more post transplant
    - Winston. *Ann Intern Med*. 2003;138:705-713.
    - Marr. *Blood* 2004 103 (4): 1527-1533
- Voriconazole, posaconazole
  - Studies underway/completed
  - Cost issues
    - Require risk based stratification

Improved diagnostics

- Consensus criteria
  - Host, microbiological and clinical factors
- Utilise radiology
- Utilise antigen testing
- Standardize molecular techniques
- Move from empirical antifungal to targeted pre-emptive approach

Improved diagnostics

- Incorporated into care pathway
  - Targeted itraconazole prophylaxis plus levels
  - Antigen and PCR testing twice weekly
  - HR CT scan within 48hrs on new chest signs or positive antigen or PCR
- Empirical antifungal to patients not on prophylaxis or with itraconazole levels <0.5 or unmeasured

醫院Aspergillosis聚集事件

Outbreaks associated with building work

Patient group	Species	Number of cases	Reference
Renal transplant	A. fumigatus	3	Arnow *et al* 1978
Renal transplant	Not specified	10	Lentino *et al* 1979
BMT	*A. fumigatus & A flavis*	10	Rotstein *et al*1985
SCBU	*A. fumigatus & Rhizopus sp*	2	Krasinski *et al* 1985
Oncology	mixed	11	Opal *et al* 1986
BMT	Not specified	5	Weems *et al 1987*
BMT	*A. fumigatus & A flavis*	6	Barnes &Rogers 1988
Radiology	Not specified	6	Hopkins *et al* 1989
ICU	*A.fumigatus*	7	Humpreys *et al* 1991
Ophthalmology	*A.fumigatus*	6	Tabbara &Al Jabarti 1998

醫療機構內侵襲性曲黴菌群聚事件實例：A醫院之經驗

- 發生時間：1996年2, 3, 9月
- 發生地點：發生在A醫院之癌症中心 (A醫院為940床的醫院，其癌症中心在隔壁一棟建築，但與醫院主建築相連)
- 此癌症中心為正壓病房，正壓每月查核一次
- 但此癌症中心的隔壁建築物正在施工
- 元兇：*A. flavus*，往常此中心感染的曲黴菌均是*A. fumigatus*

疫情調查結果: 1996

- 21/29調查案例符合“確認”或“疑似”案例
- 癌症中心日常清潔並未落實，也未用濕布進行清潔擦拭
- 單變數分析：最大的感染風險出現在靠近樓梯位置之病室
- 大量之環境檢體可很成功的檢測出*A. flavus*，但小量環境檢體則無法有效偵測

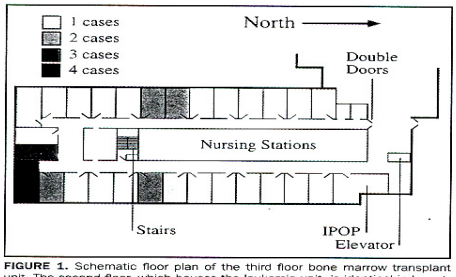


FIGURE 1. Schematic floor plan of the third floor bone marrow transplant unit. The second floor, which houses the leukemia unit, is identical in layout. The number of cases in each room is indicated by variable shading, and the cases in the two floors have been combined for the figure. Fourteen of the 21 cases were in the southeast corner of the floor, near the door to the central stairwell. The inpatient-outpatient clinic is labeled as IPOP. The entrance through the double doors is located on the northern end of the floor.

Thio CL, Smith D, Merz WG, et al. Infect Control Hosp Epidemiol 2000; 21: 18-23

疫情調查結果: 1996

- 正壓病房壓力調查
  - 25 間正壓病房中有3 間相對走廊出現負壓 (-0.35 to –3.2 Pa)
  - 中央樓梯的壓力與走廊相比出現相對正壓
  - 癌症中心內之壓力與相接鄰之醫院主建築為相對等壓或負壓

疫情出現後之環境控制策略：1996春天

- 重新評估隔離病房之正壓系統
- 病室房門改裝成能自動關閉之型態，以確保門無時無刻保持關閉
- 清潔物品表面時一定使用濕布擦拭
- 窗戶保持氣密，外牆縫隙補好

疫情出現後之環境控制策略：1996春天

- 封閉病房與外界交通之鄰近入口，並重新規劃人員進出路線
- 重新擬定病房內進行建築工事時之注意事項
- 環境採樣以偵測黴菌孢子
- 提供N95口罩給高風險病患

疫情出現後之環境控制策略：1996秋天

- 封閉骨髓移植病房與血癌病房附近之樓梯
- 以case-control方法進行疫情調查
- 進行環境採樣
- 檢查室內清潔措施
- 執行大量空氣採檢
- 環境調整若無法立即完成，可暫時以入氣HEPA過濾代替

醫院內進行建築工事之注意事項

- 必須由醫院多部門共同參予
- 建築工事進行前必須先進行感染風險評估
- 病室外建築工事時之首要注意事項
  - 保持塵埃不進入室內
- 病室內建築工事之首要注意事項
  - 不讓室內之塵埃揚起
- 個人防護
- 病例偵測及空氣採樣

病室外建築工事時之注意事項

- 保持病室內壓高於病室外
- 確保空氣濾網經常更換
- 確保病室之窗戶保持氣密，尤其是正壓隔離病房的窗戶
- 讓病房門保持常
- 以濕布擦拭灰塵
- 免疫不良的病人在病房中移轉時必須避免接觸塵埃

病室內建築工事時之注意事項

- 應避免造成灰塵飛揚、定期去除灰塵、及控制室內之溼度
  - 建築工人及工作人員必須施以勤前教育
  - 施工處必須先作安排
  - 必須通知工作人員、訪客、病患注意施工
  - 若有必要應先挪開病患及工作人員
  - 應常常監測感控措施是否落實
  - 空調與用水系統應確實保養
  - 每日進行室內清潔工作

落塵採樣之時機

- 必須達到容易採樣、快速得到結果的目標
- 用以證實空調系統是否正常運作
  - 濾網過濾效果是否正常
  - 分級由 “dirty” 到 “clean”
- 驗證進行建築工事時感控措施是否OK

Summary

- Prevention requires a multidisciplinary approach
  - Minimise exposure
  - Use targeted prophylaxis
  - Improved diagnostic techniques for pre-emptive approach
    - Clinical
    - Microbiological
    - histological
    - Radiological
- Use all available information

懇請賜教