

Schizophyllum commune as an emerging fungal pathogen: a review and report of two cases

A. Chowdhary,¹ H. S. Randhawa,¹ S. N. Gaur,² K. Agarwal,² S. Kathuria,¹ P. Roy,¹ C. H. Klaassen³ and J. F. Meis^{3,4}

Departments of ¹Medical Mycology and ²Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India, ³Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands and ⁴Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Summary

We report *Schizophyllum commune* as the aetiological agent of one case each of allergic broncho-pulmonary mycosis (ABPM) and pulmonary fungal ball, and present a literature review. The fungus was characterised by clamp connections, hyphal spicules, and formation of basidiocarps with basidiospores. The phenotypic identification was confirmed by sequencing of the ITS region. To-date, ABPM and pulmonary fungal ball to *S. commune* have been reported exclusively from Japan and North America respectively. Of the 71 globally reported cases due to *S. commune*, 45 (63%) were bronchopulmonary, 22 (31%) sinusitis and 4 extrapulmonary. Taken together, cases of bronchopulmonary disease and sinusitis numbered 67 (94%), indicating the respiratory tract as the primary target of disease. Concerning the country-wise distribution, Japan topped the list with 33 cases (46%), followed by Iran – 7 cases (10%), U.S.A. – 6 cases (9%), and a lower prevalence of 1.4–6% for the remaining 12 countries. The preponderance of the disease in Japan may be attributed to its greater awareness vis-à-vis that in other countries rather than to any geographical/climatic factors. We believe that the burden of *S. commune*-incited disease is currently underestimated, warranting comprehensive prospective studies to determine its prevalence.

Key words: *Schizophyllum commune*, allergic bronchopulmonary mycosis, fungal ball, antifungal susceptibility, India.

Introduction

Schizophyllum commune is one of the most widely distributed fleshy fungi (teleomorphic state), often found on dead and decaying organic matter, especially rotten wood of trees. It belongs to the Phylum Basidiomycota, Subphylum Agaricomycotina, Order Agaricales which contains fungi, colloquially known as mushrooms.¹ The distinctive feature of these fungi is the formation of a macroscopic fructification, the basidiocarp, that

contains basidiospores (sexual spores) developing on the outside of a club-shaped or elongate structure called the basidium.² Notwithstanding the worldwide distribution of *S. commune*, it was unknown as a human pathogen until 1950 when Kligman reported it from a case of onychomycosis.³ Recently, it has been increasingly reported as the cause of allergic broncho-pulmonary mycosis (ABPM) or other allergy-related bronchopulmonary diseases and sinusitis. Besides, invasive infections of the lung, brain, and palate in immunocompromised and immunocompetent patients have been described.⁴ In earlier publications, our laboratory has reported a novel case of ABPA with *Aspergillus terreus* and *Aspergillus fumigatus* as successive aetiological agents and two rare cases of ABPM, one caused by *Bipolaris hawaiiensis* and the second *Alternaria alternata*.^{5–7} Herein, we report for the first time from India one

Correspondence: A. Chowdhary, Department of Medical Mycology, V. P. Chest Institute, University of Delhi, Delhi 110 007, India.
Tel.: +91 11 27667560. Fax: +91 11 27666549.
E-mail: dranuradha@hotmail.com

Accepted for publication 25 February 2012

case each of ABPM and pulmonary fungal ball caused by *S. commune* and present an update of the disease. To our knowledge, the case of ABPM and of pulmonary fungal ball caused by *S. commune* is being reported for the first and the second time, respectively, from any country outside Japan.

Case 1

A 35-year-old female tailor from Bhiwani, 125 km north-west of Delhi, was referred to Vallabhbhai Patel Chest Institute (VPCI) in September 2011 for her complaints of cough with expectoration, breathlessness and wheezing since 2008, which were progressive in nature. The patient gave a history of remission of symptoms for 2–3 weeks, mostly in winter. Her expectoration was purulent, foul-smelling (quantity up to 20 ml day⁻¹) which was in the form of mucoid plugs at times. She had been exposed to passive tobacco smoke and biomass fuel smoke for almost 20 years. She did her cooking on an earthen stove fed with bagasse material procured from a nearby cane sugar-mill and stocked in the house. Previously, she had received treatment for bilateral chronic suppurative otitis media, and empirically for pulmonary tuberculosis, (regimens containing isoniazid, rifampicin, ethambutol and pyrazinamide for 6 and 9 months during 2008 and 2009 respectively) because of the presence of patchy soft opacities on her chest X-ray. She was already taking inhaled corticosteroids and long-acting β -agonists when she presented to us. Upon examination, she was found to have bilateral coarse crepitations with biphasic polyphonic rhonchi. Her haemoglobin was 13.1 g dl⁻¹, total leucocyte and differential counts – 8 200 cells μ l⁻¹, polymorphs – 56%, lymphocytes – 24%, monocytes – 5%, eosinophils – 14%, basophils – 1% and elevated absolute eosinophil count of 980 cells μ l⁻¹. The total IgE was found to be 2448 IU ml⁻¹. Serum biochemistry for renal, hepatic and blood sugar was unremarkable. Her chest X-ray revealed cystic changes with a gloved-finger sign in the left lower zone, suggesting a diagnosis of bronchiectasis (Fig. 1). This was confirmed by a contrast-enhanced high-resolution computed tomogram (CEHRCT) of the thorax, which revealed bilateral dilatation of central bronchi in all the lobes. Furthermore, the involved bronchi on the left side were also seen to be filled with hyper-attenuating mucus. The patient was then diagnosed as a case of bilateral central bronchiectasis. As saccular bronchiectasis is known to be a feature of ABPA, the patient was investigated further. Spirometry showed an FEV₁/FVC ratio of 91% of the predicted value, FVC and FEV₁ of 2.49 l and



Figure 1 Plain chest skiagram of case 1 showing the finger-in-glove sign in the left-lower zone.

2.01 l, which were 78% and 73% of the predicted values respectively. Also, after administration of a short-acting β -agonist, the FEV₁ showed an improvement by 25% and 410 ml, which suggested reversible airflow obstruction.

Mycoserological investigations

Microscopic examination of her sputum was found to be negative for acid-fast bacilli (AFB) and other bacteria. Direct microscopic examination of KOH wet mounts of three consecutive sputum specimens and the expectorated sputum/mucoid plugs demonstrated hyaline, septate and non-dichotomously branching hyphae (Fig. 2a). The sputum and mucoid plugs after homogenisation were inoculated on Sabouraud's glucose agar (SGA) and SGA supplemented with 10 μ g of benomyl per ml. On SGA with benomyl, multiple, white colonies with woolly texture were observed after 4 days at 28 °C (Fig. 2b). In contrast, contaminant moulds grew rapidly on SGA, which might have masked any potential growth of *S. commune*. The isolate was subcultured on potato dextrose agar (PDA) and incubated at 28 °C with periodic exposure to light for induction of fruiting bodies and basidiospores. A cottony white, dense mycelial growth developed with formation of basidiocarps (Fig. 2c) and basidiospores

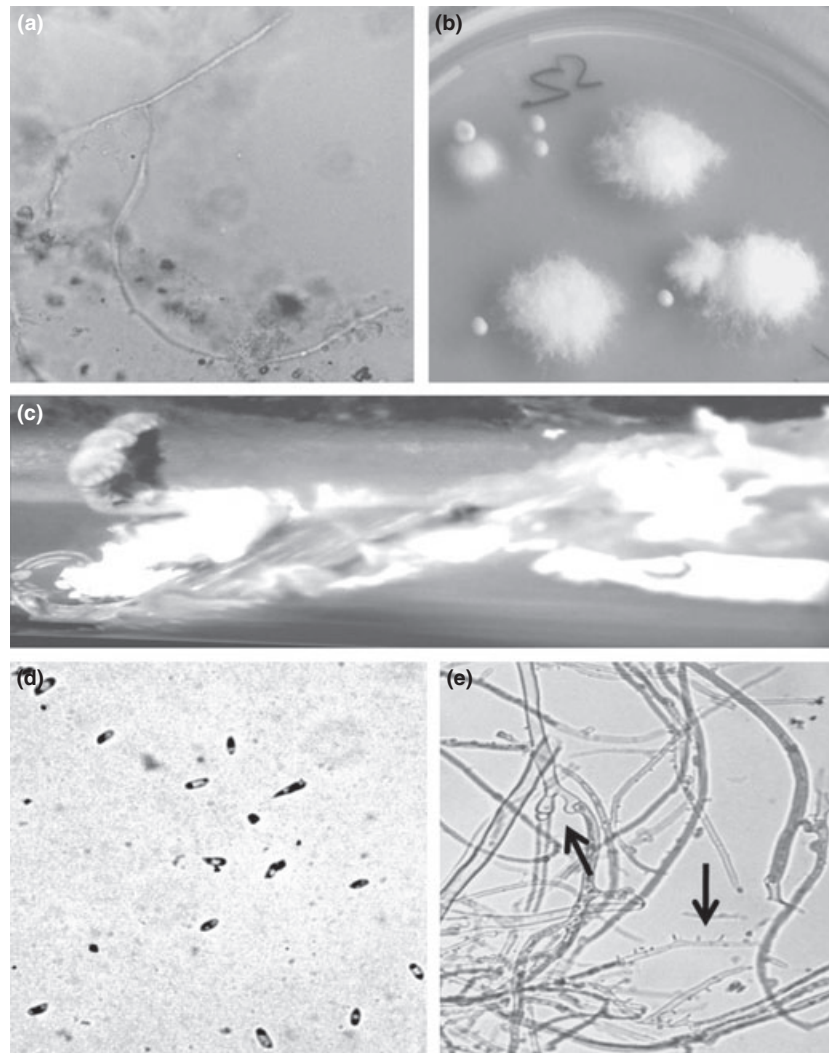


Figure 2 (a) Wet mount of a KOH-digested sputum specimen of the patient with ABPM, showing hyaline, septate and non-dichotomously branching hyphae. (b) Multiple white and woolly colonies of the *Schizophyllum commune* isolate on a SGA plate supplemented with benomyl ($10 \mu\text{g ml}^{-1}$) inoculated with sputum as seen after 4 days of incubation at 28°C . (c) Cottony white, dense mycelial growth of *S. commune* on PDA culture bottle, showing formation of a basidiocarp after 3–4 weeks of incubation at 28°C . (d) Lactophenol cotton blue mount from basidiocarp of the *S. commune* isolate on PDA, showing basidiospores, $\times 400$. (e) Slide culture of the *S. commune* isolate on malt extract agar (MEA), showing hyaline, septate hyphae with clamp connections (upward arrow) and spicules (downward arrow), $\times 400$.

(Fig. 2d) after 3–4 weeks. Slide cultures of the mould isolate on malt extract agar (MEA) revealed hyaline, septate hyphae with clamp connections and spicules (Fig. 2e) suggestive of a basidiomycetous mould. The mould isolated was assigned accession no. VPCI 279/11 (CBS 132304) for molecular identification and antifungal susceptibility testing.

Ouchterlony's immunodiffusion test

Immunodiffusion of the patient's serum collected on 27 Sept, 2011, demonstrated precipitins against the culture filtrate antigen of *S. commune* prepared as previously described for *Aspergillus* species.⁵ In contrast, negative results were found for precipitins against antigens of *Aspergillus fumigatus*, *A. flavus*, *A. terreus* and *A. niger*.

Specific IgE estimation by Enzyme-linked Immunosorbent assay (ELISA)

Schizophyllum commune extract was prepared and standardised as described earlier.⁸ Specific IgE in patients sera was determined by ELISA as previously described.⁹ Briefly, a microtitre plate (Nunc-Immuno™ modules; Thermo Fisher Scientific, Rochester, NY, USA) was coated with *S. commune* extract ($1 \mu\text{g}/100 \mu\text{l}/\text{well}$) in carbonate buffer, pH 9.6, blocked with 3% defatted milk, washed with PBST (0.1 mol l^{-1} PBS containing 0.2% Tween 20) and incubated with patient's serum or control sera ($1:10 \text{ v/v}$) at 4°C overnight. The plate was then incubated with $1:1000 \text{ v/v}$ anti-human-IgE peroxidase (Sigma, USA), colour developed with o-phenylenediamine and read at 492 nm in an ELISA reader. ELISA was

performed in triplicate and the mean of three readings was taken for analysis. Normal human sera (pooled) were used as negative control. Specific IgE binding of the patient's serum against the mycelial mat antigen from the patient's *S. commune* isolate showed an elevated IgE level, which was >fourfold higher than that of the control. Negative results were obtained with specific immunoglobulins (IgE) against *A. fumigatus* (ImmunoCap; Phadia, Uppsala, Sweden).

Skin testing

An intradermal skin test performed with the culture filtrate antigenic extract of the *S. commune* isolate elicited an induration of 20 × 15 mm, which was strongly positive compared with 10 × 10 mm elicited by histamine phosphate (base; 100 µg ml⁻¹). Besides, an Arthus type III hypersensitivity reaction was also positive.

Based on the above-mentioned observations of the patient's history, physical examination, radiology, spirometry, mycoserological and immunological investigations, a diagnosis of ABPM due to *S. commune* was made. The patient was treated with oral prednisolone in tapering doses along with inhaled corticosteroids and a long-acting β-agonist combination. Upon her review, she showed a symptomatic improvement.

Case 2

A 42-year-old man, non-smoker and hardware merchant by occupation, was referred to VPCI, Delhi, in January 2011, with complaints of occasional haemoptysis for 1 year. He had diabetes mellitus for 10 years, for which he was taking regular treatment of oral hypoglycaemics. Three years ago, the patient had been successfully treated for pulmonary tuberculosis with a 6-month-long regimen containing rifampicin, isoniazid, ethambutol and pyrazinamide. His physical examination was unremarkable except for pallor. Haemoglobin was 10.6 g dl⁻¹, total leucocyte count – 8 400 cells µl⁻¹ and differential count showed 67% polymorphs, 21% lymphocytes, 7% monocytes, 4% eosinophils and 1% basophils. Serum biochemistry revealed 6.2 g dl⁻¹ of proteins, of which albumin was 4 g dl⁻¹. Renal and hepatic parameters were within normal limits. He was shown to have fasting blood glucose of 208 mg dl⁻¹ and postprandial blood glucose of 310 mg dl⁻¹, both of which were consistent with the diagnosis of diabetes mellitus. A plain skiagram of the chest showed a non-homogenous opacity in the right upper zone. The patient underwent a CEHRCT of the thorax, which showed an 'air-crescent' sign in the apical segment of the right upper lobe, which is pathognomonic



Figure 3 Contrast-enhanced high-resolution computed tomogram (CEHRCT) of case 2 showing the 'air-crescent' sign in the apical segment of the right-upper-lobe.

of a fungal-ball in a cavity (Fig. 3). A Mantoux test with 1 tuberculin unit of purified protein derivative showed an induration of 5 × 5 mm at 48 h, which was interpreted as negative. Sputum smear examination performed on three consecutive days was found to be negative for AFB. This was confirmed by negative culture reports for *Mycobacterium tuberculosis*. Sputum culture for other bacteria was negative. A diagnosis of post-tubercular fibrocavitary disease with a fungal ball of the right upper lung lobe was made. Thereafter, six freshly expectorated serial sputum specimens were investigated in the Department of Medical Mycology, VPCI, to determine the aetiological fungus.

Mycoserological investigations

Direct microscopy of KOH wet mounts of six serial sputum specimens collected between 27 Jan to March, 2011, consistently revealed hyaline septate hyphae. In culture, sputum yielded multiple, white, woolly colonies of a mould on SGA plates incubated at 28 °C for up to 2 weeks. Slide cultures of the mould isolate on MEA revealed hyaline, septate hyphae with clamp connections and spicules compatible with *S. commune*. Cultures on PDA incubated at 28 °C with periodic exposure to light, showed dense white mycelial growth with development of basidiocarps after 2 weeks of observation. The isolate was assigned accession no. VPCI 461/11 (CBS 132305) for molecular identification and antifungal susceptibility testing.

Ouchterlony's immunodiffusion test

Immunodiffusion of the patient's serum collected on 1 August 2011, demonstrated precipitins against culture filtrate antigens prepared from the patient's *S. commune* isolate as described in case 1. In strong contrast,

negative results were found in tests using antigens of *A. fumigatus*, *A. flavus*, *A. terreus* and *A. niger*.

Specific IgE estimation by enzyme-linked immunosorbent assay (ELISA)

Specific IgE binding of the patient's serum against the mycelia mat antigen from the patient's *S. commune* isolate showed an elevated IgE level, which was >fivefold higher than that of the control.^{8,9} Negative results were obtained with specific immunoglobulins (IgE) against *A. fumigatus* (ImmunoCap).

Skin testing

An intradermal skin test was performed with the *S. commune* culture filtrate antigen (concentration 0.02 ml, 1/100 w/v). The positive control included in the test was histamine phosphate (base; 100 µg ml⁻¹), which gave an induration of 4 × 5 mm while a 1 × 1 mm induration was seen with the negative control (buffered saline). The patient showed a strongly positive result with an induration of 15 × 20 mm compared with 4 × 5 mm elicited by the positive control with histamine phosphate (base; 100 µg ml⁻¹). It was evident from these findings that the patient was suffering from post-tuberculosis fibrocavitary disease of the right upper lobe with a fungal ball due to *S. commune*. In September 2011, he was treated with tapering doses of systemic glucocorticoids (Deflazacort, Lupin, India, starting with 60 mg per day for 15 days, eventually tapered to 6 mg on alternate days) and itraconazole, 200 mg twice daily for 4 months. On his last visit in December 2011, the patient's haemoptysis had stopped and he was asymptomatic.

Molecular identification of *S. commune*

The identification of both *S. commune* isolates (VPCI 461/11 and VPCI 279/P/11, CBS 132305 and CBS 132304), originating from case 1 and case 2 were confirmed by sequencing of the ITS region (ITS-1, 5.8S rRNA and ITS-2 of rDNA). GenBank basic local alignment search tool (BLAST) searches (<http://www.ncbi.nlm.nih.gov/BLAST/Blast.cgi>) were performed for species identification. The entire ITS region sequence of both the isolates exhibited 100% identity with the corresponding sequences of *S. commune*.

Antifungal susceptibility testing

Antifungal susceptibility testing (AFST) of both the isolates of *S. commune* was performed by CLSI micro-

broth dilution.¹⁰ The antifungals tested were amphotericin B (Sigma, St. Louis, Mo, USA), fluconazole (Pfizer, Groton, CT, USA), itraconazole (Lee Pharma, Hyderabad, India), voriconazole (Pfizer), posaconazole (Schering-Plough Corp., Kenilworth, NJ, USA now Astellas), isavuconazole (Basilea Pharmaceutica International AG, Basel, Switzerland), 5-flucytosine (Sigma), caspofungin (Merck & Co Inc, Whitehouse Station, NJ, USA), micafungin (Astellas Toyama Co Ltd, Toyama, Japan) and anidulafungin (Pfizer). For the broth microdilution test, RPMI 1640 medium with glutamine without bicarbonate (Sigma) buffered to pH 7 with 0.165 mol l⁻¹ 3-N-morpholinepropanesulfonic acid (Sigma) was used. Isolates were grown on PDA for 8 days and inoculum adjusted to a final density of 1.0–5.0 × 10⁴ hyphal fragments/ml measured by spectrophotometer.¹¹ The final concentrations of the drugs were 0.125–64 µg ml⁻¹ for fluconazole and 5-flucytosine; 0.03–16 µg ml⁻¹ for amphotericin B, itraconazole, voriconazole and 0.015–8 µg ml⁻¹ for posaconazole, isavuconazole and echinocandins. Drug-free and mould-free controls were included and microtitre plates were incubated at 35 °C for 72 h. CLSI recommended quality control strains, *Candida krusei*, ATCC 6258, and *Candida parapsilosis*, ATCC 22019, and reference strains, *Aspergillus fumigatus* ATCC 204305 and *Aspergillus flavus* ATCC 204304 were included. The MIC end points were read visually which, for azoles and amphotericin B, were defined as the lowest concentration at which there was 100% inhibition of growth compared with the drug-free control wells. For echinocandins, minimal effective concentration (MEC) was defined as the lowest concentration of drug that led to the growth of small, rounded and compact hyphal forms. The isolates had lowest MIC of posaconazole with range of 0.015–0.125 µg ml⁻¹ followed by itraconazole (<0.06–0.125 µg ml⁻¹), isavuconazole (0.125–0.25 µg ml⁻¹) and (0.5–1 µg ml⁻¹) of voriconazole and amphotericin B. All three echinocandins showed good activity (MEC, 0.125–0.5 µg ml⁻¹).

Discussion

The salient features of case 1 and case 2 (Table 1) fulfil the clinical and laboratory criteria required for their definitive diagnosis. The phenotypic description of the two *S. commune* isolates is compatible with the species, which is confirmed by sequencing of the entire ITS region. To date, only two cases of sinusitis due to *S. commune* from India, one from Chennai (Tamil Nadu) and another from Bhubaneswar (Odisha) have been reported.^{12,13}

Table 1 Salient clinical and laboratory diagnostic features of Case 1 (ABPM) and Case 2 (pulmonary fungal ball) due to *Schizophyllum commune*.

Clinical category, Age/sex	Past history	Sputum plugs	Isolation of <i>S. commune</i>	Eosino- philia	Skin test type		Serum precipitins (specific IgG)	Elevated total IgE	Elevated specific IgE	Radiology		Therapy and response
					I	III				X-ray	CT scan	
ABPM, 35 y/F	Asthma	+	+	+	+	+	+	+	>fourfold higher than the control	Fleeting infiltrates, gloved-finger sign	Bilateral central bronchiectasis, hyper-attenuating mucus impaction	Tapering doses of deflazocort, symptomatic improvement
Pulmonary fungal ball, 42 y/M	Pulmonary tuberculosis	-	+	ND ¹	+	+	+	ND ¹	>fivefold higher than the control	Non-homogenous opacity in right upper zone	Cavity with air-crescent sign in right upper lobe, apical segment	Tapering doses of deflazocort with itraconazole (200 mg twice a day), symptomatic improvement

¹ND, not done.

ABPM is a form of hypersensitivity lung disease with multiple aetiological agents that is diagnosed by the criteria recommended by Rosenberg *et al.* [14,15]. The commonest aetiological agent is *A. fumigatus* but rarely other species of *Aspergillus*, *Bipolaris*, *Curvularia*, *Drechslera*, *Penicillium*, *Stemphyllium*, *Scedosporium* etc., as well as the opportunistic yeast pathogens, *C. albicans* and *C. glabrata* have been reported as aetiological agents.^{16–25} The first report, attributing a probable pathogenic role to *S. commune* was by Kligman (1950) in a case of onychomycosis.³ In 1955, Chavez-Batista *et al.* [26] from Brazil described a case of meningitis (basidiomycosis) due to *S. commune*. This was followed by a report in 1956 on the isolation of *S. commune* on three different occasions from sputum of a patient with a lung disorder by Ciferri *et al.* [27] The pathogenic potential of *S. commune* was experimentally demonstrated in 1971 by Greer and Bolanos, using Swiss white mice, fragmented hyphal inoculum and an intraperitoneal route of infection.²⁸ The fungus was found to be more pathogenic to weaning mice than to adults. Treatment of the mice with either cortisone or mucin or both rendered the mice highly susceptible, causing 75% fatalities with histological lesions in the lungs, lymph nodes, liver and subcutaneous tissue. Interestingly, tissue sections from the various organs revealed penetration of parenchyma by hyphae possessing clamp connections. In 1973, a case of ulceration with perforation of the palate in a 4-month old girl, caused by *S. commune*, was described by Restrepo *et al.* [29] The afore-mentioned early publications on *S. commune* were critically reviewed in 1978 by Greer.³⁰ In view of the paucity of early clinical reports, *S. commune* was regarded as a rare human pathogen. More recently, however, it seems to have emerged as an increasingly important pathogen, which incites a wide array of clinical disease manifestations that include invasive as well as non-invasive diseases. In this context, attention is called to the statement in 1996 by Rihs *et al.* [31] who pointed out that the number of cultures identified as *S. commune* by the Fungus Reference Laboratory of the Centers for Disease Control, Atlanta, USA, had gone up to 16 isolates in 2 years. Supportive evidence for the pathogenic potential of *S. commune* has been provided by Unno *et al.* [32] who developed a murine model of invasive pulmonary and systemic basidiomycosis due to *S. commune*, employing basidiospores as inoculum and the intratracheal route of infection in immunosuppressed mice. All of the immunosuppressed mice died within 2 weeks due to a massive disseminated fungal infection, suggesting a much higher virulence of the fungus than was previously assumed.

We believe that the available reports on *S. commune*-incited disease cannot be taken to truly reflect the magnitude of morbidity and mortality caused by this basidiomycetous respiratory pathogen. This viewpoint is supported by the fact that *S. commune* is inhibited on culture media fortified with cycloheximide, it has no asexual reproduction and, as a result, it grows as sterile, dense, white to tan mould colonies for many days in primary cultures, which hinders its identification. Clamp connections and lateral tubercles or spicules on hyphae that characterise the growth of this fungus may be missed during microscopy or may not develop in certain isolates.^{31,33–35} This adds to the difficulties of early identification of the species in culture. Furthermore, *S. commune* develops its characteristic fructifications, i.e. basidiocarps and basidiospores (teleomorphic/sexual state) only when the cultures are incubated longer with periodic exposure to light, and that too when the isolated strain is dikaryotic or mated with a compatible monokaryotic strain. As diagnostic microbiology laboratories rarely retain the cultures beyond a few days for observation, *S. commune* is likely to be overlooked and discarded as an extraneous mould. These difficulties are likely to result in misdiagnosis, leading to administration of incorrect therapy, which may complicate or jeopardise the patient's recovery.

The striking diversity of clinical manifestations of the disease due to *S. commune* (Table 2) underscores the versatility of this pathogen.^{3,12,13,26,29,31,33–70} At one end, it has been implicated in the aetiology of onychomycosis, while at the other, it is recognised as the aetiological agent of a variety of hypersensitivity disorders, such as allergic sinusitis, bronchopulmonary mycoses, bronchial mucoid impaction, chronic eosinophilic pneumonia, etc., and of invasive infections, such as fatal disseminated infections involving the lungs and brain.^{31,53,55,62,65,69,70} Our literature search has revealed that, barring one preliminary report, prospective studies on *S. commune* infections are lacking.⁶⁸ Of 71 cases of various clinical entities due to *S. commune* distributed worldwide, 45 (63%) were bronchopulmonary disease, 22 (31%) – sinusitis and only 4 (6%) were extra-pulmonary (Table 2). Interestingly, one of the 19 cases of ABPM from Japan had a dual aetiology, i.e. it was concomitantly caused by *S. commune* and *A. fumigatus*. We are aware of only one previous case of ABPM with dual fungal aetiology. That was a case of ABPA in which *A. terreus* and *A. fumigatus* were successive aetiological agents.⁵ Taken together, the cases of bronchopulmonary disease and sinusitis numbered 67 i.e. 94% of the 71 globally reported cases. Thus, the respiratory tract is probably the primary

Table 2 Clinical spectrum of fungal disease due to *Schizophyllum commune* and country-wise distribution of clinical cases (*n* = 71).

Mycoses (No. of cases)	Country (No. of cases)	References
Sinusitis (22)	Austria (4)	[33]
	USA (4)	[34,36,37]
	Colombia (3)	[38–40]
	France (3)	[41–43]
	Serbia (2)	[44,45]
	India (2)	[12,13]
	U.K. (1)	[46]
	Japan (1)	[47]
	Australia (1)	[48]
	New Zealand (1)	[35]
Allergic broncho-pulmonary mycosis (20)	Japan (19)	[49–58]
Bronchial mucoid impaction (5)	India (1)	Present study
Pulmonary fungal ball (2)	Japan (5)	[53,59–62]
<i>Schizophyllum</i> asthma (2)	North America (1)	[63]
	India (1)	Present study
Pulmonary infiltrate plus eosinophilia (1)	Japan (2)	[64]
Chronic eosinophilic pneumonia (1)	Japan (1)	[53]
Honeycomb lung (1)	Japan (1)	[65]
Bronchogenous cyst (1)	Japan (1)	[66]
Other pulmonary mycoses (12)	Serbia (1)	[67]
	Iran (7)	[68]
	Japan (3)	[53]
	Taiwan (1)	[69]
	Italy (1)	[70]
Extra pulmonary mycoses (4) ¹	U.S.A. (2)	[3,31]
	Brazil (1)	[26]
	Colombia (1)	[29]

¹includes one case each of onychomycosis, fatal brain abscess, meningitis and ulceration of palate with perforation.

target of the disease due to *S. commune*. This is in consonance with the fact that the pathogen has a widespread environmental prevalence, growing on dead or decaying wood and other vegetable matter. At maturity, its fructifications or basidiocarps release the basidiospores into the atmosphere which get inhaled by the population and may initiate the disease in the nose or the bronchopulmonary tree. Depending upon the host immunity or other factors, such as the extent of exposure to the fungus, the infection may remain localised or get disseminated from the primary site to other organs of the body.

The country-wise prevalence of mycoses due to *S. commune* is depicted in Fig. 4. Japan tops the list of 15 countries, with 33 out of 71 cases, i.e. a prevalence of 46%. This is followed by Iran – 7 cases (10%), U.S.A. – 6 cases (9%), Colombia, Austria and India – 4 cases (6%) each, France and Serbia – 3 cases (4%) each, Brazil, Italy, U.K, North America, Taiwan, Australia and New Zealand – one case (1.4%) each. The preponderance of

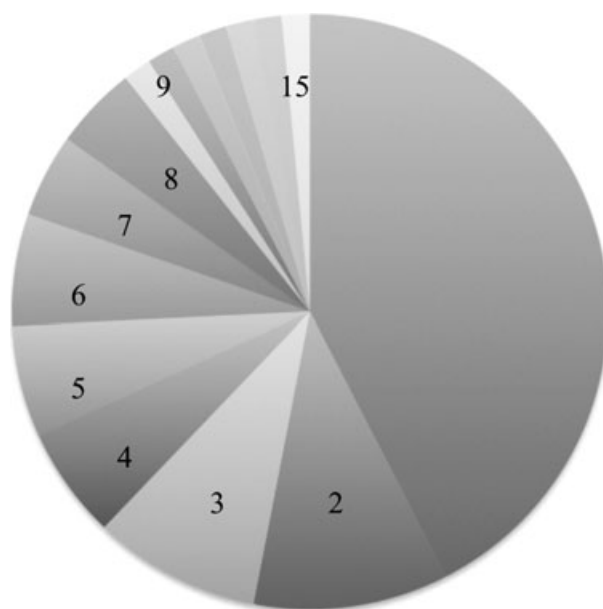


Figure 4 Country-wise occurrence (%) of mycoses due to *Schizosphaera commune*: A – Japan (46%), B – Iran (10%), C – USA (9%), D – Austria (6%), E – Colombia (6%), F – India (6%), G – France (4%), H – Serbia (4%), I – Australia (1.4%), J – Brazil (1.4%), K – Italy (1.4%), L – New Zealand (1.4%), M – Taiwan (1.4%), N – U.K. (1.4%), O – North America (1.4%). Note the preponderance of disease in Japan.

cases in Japan may be ascribed to the greater awareness of the disease and familiarity with the diagnostic morphology of its aetiological agent among the Japanese clinicians and microbiologists vis-à-vis those from other countries, rather than to any geographical/climatic factors unique to this South-East Asian country favouring this fungus. Currently, there is no information on the isolation of *S. commune* from any clinical material in the African continent.

Information on the prevalence of *S. commune* infections in animals is limited to a few sporadic case reports in canines from Japan. The first case was a 3-year-old mongrel dog, showing a granulomatous lesion in the neck, which was unsuccessfully treated with oral ketoconazole for 3 months, but the animal died.⁷¹ The second case was of a 6-year-old Labrador retriever with osteomyelitis in her hind legs. It was successfully treated with itraconazole to which the canine *S. commune* isolate was found to be susceptible by *in vitro* testing.⁷²

The role of antifungal therapy in cases of ABPM and pulmonary fungal ball due to *S. commune* remains unclear because of the rarity of reports on these clinical entities and consequently a limited experience with their chemotherapeutic management. Case 1 of our study (ABPM) showed symptomatic improvement in response

to oral and inhaled corticosteroids. Case 2, a diabetic with pulmonary fungal ball, received itraconazole, but a long-term follow-up is required in order to evaluate the therapeutic value of this antifungal azole. *In vitro* susceptibility tests on both of our clinical isolates of *S. commune* demonstrated low MIC/MEC's for amphotericin B, caspofungin, micafungin, anidulafungin and all of the azoles including the new drug isavuconazole. Data on *in vitro* antifungal sensitivity testing of *S. commune* are scarce. One available report is by Gonzalez *et al.* [11] and our results are in agreement with them concerning the susceptibility to itraconazole, voriconazole and amphotericin B of their 5 test clinical isolates of *S. commune*. Further studies on *in vitro* antifungal susceptibilities of a large number of *S. commune* isolates are indicated for a more efficacious antifungal therapy for this emerging fungal pathogen.

Acknowledgments

The work was carried out, in part, with financial assistance from the Indian Council of Medical Research, New Delhi (HIV/50/107/2008). H.S.R. acknowledges the award of an Honorary Scientist position by the Indian National Science Academy, New Delhi.

Declaration of interest: JFM received grants from Astellas, Merck, Basilea and Schering-Plough. He has been a consultant to Basilea and Merck, and received speaker's fees from Merck, Pfizer, Schering-Plough, Gilead and Janssen Pharmaceutica. CHK received grants from Pfizer. All other authors: no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- Hibbett DS, Binder M, Bischoff JF *et al.* A higher-level phylogenetic classification of the fungi. *Mycol Res* 2007; **111**: 509–47.
- de Hoog GS, Guarro J, Gene J, Figueras MJ. *Atlas of Clinical Fungi*. Utrecht/Reus: CBS/Universitat Rovira I Virgili, 2000.
- Kligman AM. A basidiomycete probably causing onychomycosis. *J Invest Dermatol* 1950; **14**: 67–70.
- Sigler L. Miscellaneous opportunistic fungi. In: Howard DH (ed.), *Pathogenic Fungi in Humans and Animals*. New York, Basel: Marcel Dekker, Inc., 2003: 637–76.
- Khan ZU, Sandhu RS, Randhawa HS, Jain SK, Kowshik T. *Aspergillus terreus* and *Aspergillus fumigatus* as successive etiologic agents in a patient with allergic bronchopulmonary aspergillosis. *J Mycol Med* 2000; **10**: 158–61.
- Chowdhary A, Randhawa HS, Singh V *et al.* *Bipolaris hawaiiensis* as etiologic agent of allergic bronchopulmonary mycosis: first case in a paediatric patient. *Med Mycol* 2011; **49**: 760–5.

- 7 Chowdhary A, Agarwal K, Randhawa HS *et al.* A rare case of allergic bronchopulmonary mycosis caused by *Alternaria alternata*. *Med Mycol* 2012 (accepted).
- 8 Shanker J, Singh BP, Gaur SN, Arora N. Engineered Alt a 13 fragment of *Alternaria alternata* abrogated IgE binding without affecting T cell stimulation. *J Clin Immunol* 2009; **29**: 63–70.
- 9 Nair S, Kukreja N, Singh BP, Arora N. Identification of B cell epitopes of alcohol dehydrogenase allergen of *Curvularia lunata*. *PLoS ONE* 2011; **6**: e20020 doi:10.1371/journal.pone.0020020.
- 10 Clinical and Laboratory Standards Institute. *Reference Method for Broth Dilution Antimicrobial Susceptibility Testing of Filamentous Fungi*, 2nd edn. Approved Standard M38-A2. Wayne, PA, USA: CLSI, 2008.
- 11 Gonzalez GM, Sutton DA, Thompson E, Tejerina R, Rinaldi MG. In vitro activities of approved and investigational antifungal agents against 44 clinical isolates of basidiomycetous fungi. *Antimicrob Agents Chemother* 2001; **45**: 633–5.
- 12 Premamalini T, Ambujavalli BT, Anitha S, Somu L, Kindo AJ. *Schizophyllum commune* a causative agent of fungal sinusitis: a case report. *Case Reports Infect Dis* 2011. doi: 10.1155/2011/821259.
- 13 Swain B, Panigrahy R, Panigrahi D. *Schizophyllum commune* sinusitis in an immunocompetent host. *Indian J Med Microbiol* 2011; **29**: 439–42.
- 14 Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; **86**: 405–14.
- 15 Martin T, Chetty A. Allergic fungal diseases of the lung: pathology. In: Kurup VP (ed.), *Mold Allergy, Biology and Pathogenesis*. Trivandrum, Kerala (India): Research Signpost, 2005: 163–73.
- 16 Sahn SA, Lakshminarayan S. Allergic bronchopulmonary penicilliosis. *Chest* 1973; **63**: 286–8.
- 17 Sandhu RS, Mehta SK, Khan ZU, Singh MM. Role of *Aspergillus* and *Candida* species in allergic bronchopulmonary mycoses: a comparative study. *Scand J Respir Dis* 1979; **60**: 235–42.
- 18 Bantar SR, Allan B, Hewitson RP, Don PA. Allergic bronchopulmonary stemphyliosis. *Thorax* 1980; **35**: 515–8.
- 19 McAleer R, Kroenert DB, Elder JL, Froudast JH. Allergic bronchopulmonary disease caused by *Curvularia lunata* and *Drechslera hawaiiensis*. *Thorax* 1981; **36**: 338–44.
- 20 Hendrick DJ, Ellithorpe DB, Lyon F, Hattier P, Salvaggio JE. Allergic bronchopulmonary helminthosporiosis. *Am Rev Respir Dis* 1982; **126**: 935–8.
- 21 Patterson R, Samuels BS, Phair JJ, Roberts M. Bronchopulmonary torulopsosis? *Int Arch Allergy Appl Immunol* 1982; **69**: 30–3.
- 22 Pinson P, Van der Straeten M. Fibrotic stage of allergic bronchopulmonary candidiasis. *Chest* 1991; **100**: 565–7.
- 23 Travis WD, Kwon-Chung KJ, Kleiner DE *et al.* Unusual aspects of allergic bronchopulmonary fungal disease: report of two cases due to *Curvularia* organisms associated with allergic fungal sinusitis. *Hum Pathol* 1991; **22**: 1240–8.
- 24 Saenz RE, Brown WD, Sanders CV. Allergic bronchopulmonary disease caused by *Bipolaris hawaiiensis* presenting as a necrotizing pneumonia: case report and review of literature. *Am J Med Sci* 2000; **321**: 209–12.
- 25 Cortez KJ, Roilides E, Quiroz-Telles F *et al.* Infections caused by *Scedosporium* spp. *Clin Microbiol Rev* 2008; **21**: 157–97.
- 26 Chavez-Batista A, Maica JA, Singer R. Basidio-neuromycosis on man. *Anals da Sociedade de Biologia de Pernambuco* 1955; **13**: 52–60.
- 27 Ciferri RA, Chavez-Batista A, Campos S. Isolation of *Schizophyllum commune* from sputum. *Atti dell Instituto Botanico e Laboratoria Crittogamico di Pavia* 1956; **14**: 3–5.
- 28 Greer DL, Bolanos B. Pathogenic potential of *Schizophyllum commune* isolated from a human case. *Sabouraudia* 1971; **12**: 233–44.
- 29 Restrepo A, Greer DL, Robledo M, Osorio O, Mondragon H. Ulceration of the palate caused by a basidiomycete *Schizophyllum commune*. *Sabouraudia* 1973; **11**: 201–4.
- 30 Greer DL. Basidiomycetes as agents of human infections: a review. *Mycopathologia* 1978; **65**: 133–9.
- 31 Rihs JD, Padhye AA, Good CB. Brain abscess caused by *Schizophyllum commune*: an emerging basidiomycete pathogen. *J Clin Microbiol* 1996; **34**: 1628–32.
- 32 Unno H, Kamei K, Honda A, Nishimura K, Kuriyama T. A murine model of pulmonary basidiomycosis by *Schizophyllum commune*. *J Infect Chemother* 2005; **11**: 136–40.
- 33 Buzina W, Lang-Loidolt D, Braun H, Freudenschuss K, Stammlerberger H. Development of molecular methods for identification of *Schizophyllum commune* from clinical samples. *J Clin Microbiol* 2001; **39**: 2391–6.
- 34 Roh ML, Tuazon CU, Mandler R, Kwon-Chung KJ, Geist CE. Sphenocavernous syndrome associated with *Schizophyllum commune* infection of the sphenoid sinus. *Ophthal Plast Reconstr Surg* 2005; **21**: 71–4.
- 35 Sigler L, Bartley JR, Parr DH, Morris AJ. Maxillary sinusitis caused by medusoid form of *Schizophyllum commune*. *J Clin Microbiol* 1999; **37**: 3395–8.
- 36 Kern ME, Uecker FA. Maxillary sinus infection caused by the homobasidiomycetous fungus *Schizophyllum commune*. *J Clin Microbiol* 1986; **23**: 1001–5.
- 37 Rosenthal J, Katz R, DuBois DB, Morrissey A, Machicao A. Chronic maxillary sinusitis associated with the mushroom *Schizophyllum commune* in a patient with AIDS. *Clin Infect Dis* 1992; **14**: 46–8.
- 38 Sigler L, Estrada S, Montealegre NA *et al.* Maxillary sinusitis caused by *Schizophyllum commune* and experience with treatment. *J Med Vet Mycol* 1997; **35**: 365–70.
- 39 Jiménez R, Rodrigues C, Arango M, De Bedout C, Restrepo A. Sinusitis por *Schizophyllum commune*: informe de nueve casos. *Infectio* 2002; **6**: 108.
- 40 Castro LÁ, Álvarez MI, Martínez E. Case report of *Schizophyllum commune* sinusitis in an immunocompetent patient. *Colomb Med* 2010; **41**: 71–5.
- 41 Marlier S, De Jaureguiberry JP, Aguilon P, Carloz E, Duval JL, Jaubert D. Chronic sinusitis caused by *Schizophyllum commune* in AIDS. *Presse Med* 1993; **22**: 1107.
- 42 Baron O, Cassaing S, Percodani J *et al.* Nucleotide sequencing for diagnosis of sinus infection by *Schizophyllum commune*, an uncommon pathogenic fungus. *J Clin Microbiol* 2006; **44**: 3042–3.
- 43 Lorentz C, Rivier A, Debourgogne A *et al.* Ethmoido-maxillary sinusitis caused by the basidiomycetous fungus *Schizophyllum commune*. *Mycoses* 2012; **55**: e8–12.
- 44 Pekic S, Arsenijevic VA, Gazibara MS *et al.* What lurks in the cellar? *Lancet* 2010; **30**: 375–432.
- 45 Perić A, Vojvodić D, Zolotarevski L, Perić A. Nasal polyposis and fungal *Schizophyllum commune* infection: a case report. *Acta Medica (Hradec Kralove)* 2011; **54**: 83–6.

- 46 Clark S, Campbell CK, Sandison A, Choa DI. *Schizophyllum commune*: an unusual isolate from a patient with allergic fungal sinusitis. *J Infect* 1996; **32**: 147–50.
- 47 Taguchi K, Oharaseki T, Yokouchi Y *et al.* Allergic fungal sinusitis caused by *Bipolaris spicifera* and *Schizophyllum commune*. *Med Mycol* 2007; **45**: 559–64.
- 48 Shaw CL, McCleave M, Wormald PJ. Unusual presentations of isolated sphenoid fungal sinusitis. *J Laryngol Otol* 2000; **114**: 385–8.
- 49 Kamei K, Unno H, Nagao K, Kuriyama T, Nishimura K, Miyaji M. Allergic bronchopulmonary mycosis caused by the basidiomycetous fungus *Schizophyllum commune*. *Clin Infect Dis* 1994; **18**: 305–9.
- 50 Tomita K, Hashizume I, Kasamatsu N *et al.* Allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Nihon Kyobu Shikkan Gakkai Zasshi* 1996; **34**: 804–9.
- 51 Ikushima S. Case of allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Jpn J Antibiot* 1997; **50**: 47–9.
- 52 Yamashina S. Case of allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Jpn J Antibiot* 1997; **50**: 51–3.
- 53 Kamei K, Unno H, Ito J, Nishimura K, Miyaji M. Analysis of the cases in which *Schizophyllum commune* was isolated. *Nihon Ishinkin Gakkai Zasshi* 1999; **40**: 175–81.
- 54 Yamasaki A, Nishimura K, Sano H *et al.* A case of allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Arerugi* 2002; **51**: 439–42.
- 55 Kawano T, Matsuse H, Iida K *et al.* Two cases of allergic bronchopulmonary mycosis caused by *Schizophyllum commune* in young asthmatic patients. *Nihon Kokyuki Gakkai Zasshi* 2003; **41**: 233–6.
- 56 Amemiya Y, Shirai R, Tokimatsu I *et al.* Allergic bronchopulmonary mycosis induced by *Schizophyllum commune*—case report and review of the literature. *Nihon Kokyuki Gakkai Zasshi* 2009; **47**: 692–7.
- 57 Masunaga A, Morimoto K, Ando T, Ikushima S, Takemura T, Oritsu M. Three cases of allergic bronchopulmonary mycosis due to *Schizophyllum commune*. *Nihon Kokyuki Gakkai Zasshi* 2010; **48**: 912–7.
- 58 Ishiguro T, Takayanagi N, Saito A *et al.* Allergic bronchopulmonary mycosis due to *Schizophyllum commune* and *Aspergillus fumigatus*. *Nihon Kokyuki Gakkai Zasshi* 2011; **49**: 612–8.
- 59 Amitani R, Nishimura K, Niimi A *et al.* Bronchial mucoid impaction due to the monokaryotic mycelium *Schizophyllum commune*. *Clin Infect Dis* 1996; **22**: 146–8.
- 60 Miyazaki Y, Sakashita H, Tanaka T, Kamei K, Nishimura K, Yoshizawa Y. Mucoid impaction caused by monokaryotic mycelium of *Schizophyllum commune* in association with bronchiectasis. *Intern Med* 2000; **39**: 160–2.
- 61 Itou Y, Sasaki S, Watanabe S *et al.* A case of mucoid impaction of bronchi (MIB) due to *Schizophyllum commune*. *Nihon Kokyuki Gakkai Zasshi* 2001; **39**: 266–70.
- 62 Ishiguro T, Takayanagi N, Tokunaga D *et al.* Pulmonary *Schizophyllum commune* infection developing mucoid impaction of the bronchi. *Yale J Biol Med* 2007; **80**: 105–11.
- 63 Sigler L, de la Maza LM, Tan G, Egger KN, Sherburne RK. Diagnostic difficulties caused by a nonclamped *Schizophyllum commune* isolate in a case of fungus ball of the lung. *J Clin Microbiol* 1995; **33**: 1979–83.
- 64 Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Two cases of *Schizophyllum* asthma: is this a new clinical entity or a precursor of ABPM? *Pulm Pharmacol Therapeut* 2011; **24**: 559–62.
- 65 Kawayama T, Fujiki R, Rikimaru T, Aizawa H. Chronic eosinophilic pneumonia associated with *Schizophyllum commune*. *Respirology* 2003; **8**: 529–31.
- 66 Iizasa T, Kamei K, Chiyo M *et al.* Colonization with *Schizophyllum commune* of localized honeycomb lung with mucus. *Respiration* 2001; **68**: 201–3.
- 67 Bulajic N, Cvijanovic V, Vukojevic J, Tomic D, Johnson E. *Schizophyllum commune* associated with bronchogenous cyst. *Mycoses* 2006; **49**: 343–5.
- 68 Chadeganipour M, Bonerje G, Nilipour S. Detection of antibodies in immunocompromised patients affected with pulmonary *Schizophyllum* infection. *Clin Immunol* 2010; **135**: S74 (Abstract). doi: 10.1016/j.clim.2010.03.224.
- 69 Roan JN, Hsieh HY, Tsai HW *et al.* Pulmonary nodules caused by *Schizophyllum commune* after cardiac transplantation. *J Infect* 2009; **58**: 164–7.
- 70 Tullio V, Mandras N, Banche G *et al.* *Schizophyllum commune*: an unusual agent bronchopneumonia in an immunocompromised patient. *Med Mycol* 2008; **46**: 735–8.
- 71 Kano R, Oomae S, Nakano Y *et al.* First report on *Schizophyllum commune* from a dog. *J Clin Microbiol* 2002; **40**: 3535–7.
- 72 Tanaka H, Takizawa K, Baba O *et al.* Basidiomycosis: *Schizophyllum commune* osteomyelitis in a dog. *J Vet Med Sci* 2008; **70**: 1257–9.