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Contents

Laboratory diagnosis of skin infections – a clinician's perspective

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The current article was written according to the content of the CME activity "Laboratory diagnosis of skin infections – a clinician's perspective. Seminar on Infectious Diseases: Diagnosing common infections in the general practice" organised by Princess Margaret Hospital, Hong Kong Medical Association, and Hong Kong Society for Infectious Diseases held on 5 July 2008.

Introduction

Cutaneous infections can be classified according to the aetiological agents. The infective agents include viruses, bacteria, fungi, algae, and parasites. These organisms may cause dermatological conditions that do not involve tissue invasion. On the other hand, the skin surface is the habitat of many commensal microbes and is liable to environmental contamination. Mere isolation of these microorganisms from clinical specimens taken from the skin surface are not *sine qua non* to their role in disease causation. The laboratory approach to these cutaneous conditions may involve answering the following 3 questions: 1) What is the purpose of performing the laboratory tests under consideration? 2) Which is the most appropriate laboratory test? 3) How to interpret the laboratory

results in the concerned clinical context? To better inform the laboratory microbiologists, it is prudent to provide the essential clinical information and specify the organisms of interest on the request form.

Bacterial diseases

Examples of the common bacterial skin infections encountered in the primary care settings may include: pyodermatous conditions (impetigo, folliculitis, furuncle, carbuncle, ecthyma, etc), secondary infected eczema and wound infection. A standard swab can be used to help isolate the causative organism involved in the concerned pyodermatous skin diseases. The swabs should be sent to the laboratory within 2 days. A direct Gram smear can be performed at the "bed-side". The common bacteria that cause these conditions are the Gram-positive cocci: the streptococci and staphylococci. Demonstration of host response i.e. presence of polymorphonuclear cells in the Gram smear is a clue that there is true tissue invasion and is helpful to establish the diagnosis of secondary infection in the clinical context of wound and eczema. The presence of intracellular organism such as Gram-positive cocci can be regarded as diagnostic in these conditions.

Erythrasma and pitted keratolysis are the other two common dermatological conditions encountered in primary care settings. These conditions are related to *coryneforms* (i.e. *diphtheroids*). As these *coryneforms* are common skin commensals and tissue invasion is not involved in the pathogenesis of these conditions, the best way to establish the diagnosis is by clinical examination (± under Wood's light in erythrasma). Laboratory tests are only indicated to exclude the other differential diagnoses, commonly dermatophyte infections.

Fungal diseases

Dermatophytes, and yeasts of *Malassezia* and *Candida* species are common fungi that cause superficial skin diseases.

Superficial skin infections caused by the dermatophytes are better known as tinea. Tinea pedis is one of the most common conditions encountered in the community settings. Common dermatophytes that cause human disease are: *Trichophyton*, *Microsporum* and *Epidermophyton* species. These fungi live on keratin and have different sites of predilection. They can also be classified according to their source of acquisition when human diseases are of concern as anthropophilic, zoophilic and geophilic when the sources are other humans, animals and soil/vegetable matters respectively[1]. The laboratory diagnostic approach will involve 1) wet mount KOH examination that can be performed rapidly at the "bed-side" with or without staining (e.g. by Parker's blue black ink), 2) culture for proper species identification.

Scales from active lesions produced by skin scraping can be collected and wrapped in colour paper (and put in a properly sealed container) and sent to the supporting laboratory by mail. Cleansing of the site may be required in those grossly contaminated sites such as from a "dirty" foot before performing skin scraping. Diseased hair should be plucked (not cut) in those cases of suspected tinea capitis. Subungual hyperkeratotic material should be collected with a curette in those cases of suspected onychomycosis. Sampling should also be collected as proximal as possible in those cases of clinical distal lateral subungual onychomycosis. Simple nail clipping of the distal diseased nail may not give the maximum yield. Repeated sampling is sometimes required to isolate the causative fungi. Two types of media, one with and the other without cycloheximide, are ideally used to culture nail sample[2]. The one with cycloheximide will suppress the growth of the non-dermatophyte filamentous fungi and hence enhance the growth of the dermatophytes. Whereas the one without

will allow the growth of the non-dermatophyte filamentous fungi, some of which may sometimes cause skin diseases.

Pityriasis versicolor is another common skin disease encountered in primary care. It is caused by yeasts of *Malassezia* species. As *Malassezia* species can be detected in many asymptomatic individuals and only cause disease when these yeasts are in certain phase of growth or metabolism, the best way to establish the diagnosis is by clinical examination (which can be assisted by Wood's light). Diagnosis can also be made with the help of KOH wet mount examination of the scales. The classic 'spaghetti and meat ball' pattern can be demonstrated by microscopic examination of the wet mount. Fungal culture is not indicated in this clinical setting.

Candida species cause a variety of cutaneous diseases. These include orogenital infection, intertriginous infection, chronic paronychia, diaper infection, in addition to other more serious infections affecting the predisposed hosts. Diagnosis can also be made with the help of Gram staining of relevant clinical samples. Demonstration of yeasts with pseudohyphae formation is regarded as diagnostic of tissue invasion and hence genuine clinical disease. Fungal culture can be performed but results have to be interpreted in clinical context.

Viral diseases

Wart, molluscum contagiosum and cutaneous herpes infection are common viral diseases of the skin. In real practice, diagnosis is mostly made only by clinical assessment. The wart virus and pox virus (the causative virus of molluscum) cannot be grown in viral culture system. Laboratory confirmation is not usually required. Molecular diagnostics which are applicable in cervical diseases related to wart virus infection are not applicable in infection involving the glabrous skin outside research settings. Skin biopsy and histology may be performed to establish the diagnosis in selected cases.

Most skin diseases caused by herpes simplex and varicella-zoster virus can be made by clinical examination. Viral culture is still the gold standard for laboratory confirmation of these infections. Tzanck smear of samples from the vesicular lesions of these infections can be used to give a quick result. Tzanck smear can be performed at the "bed-side". Tzanck smear however is not able to differentiate if the lesion is caused by the type 1 or type 2 herpes simplex virus or varicella-zoster virus. Depending on the availability of facilities, direct immunofluorescence examination of the smear taken from clinical samples can give a very quick result. Nucleic acid amplification test that is available in some major hospitals is not usually applied in the clinical context of simple cutaneous infections. Serological test for herpes simplex infection should be used with extreme caution as only a few of these tests are US FDA approved as type specific i.e. able to differentiate between type 1 and 2 infection (and a confirmation protocol is recommended by the manufacturer)[3]. It is estimated that about 90% of the adult population in Hong Kong have been infected with HSV-1 virus by 30 years of age. The presence of a positive serology may or may not explain the active clinical disease of concern.

Conclusion

Laboratory tests can help establish the diagnosis of a variety of common cutaneous infections. Initiation and interpretation of these tests should be made in the appropriate clinical context. These tests cannot replace the clinical acumen of physicians.

Disclaimer: All opinions expressed are the authors' and do not represent the views of Social Hygiene Service, Public Health Service Branch nor Centre for Health Protection

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Literature review on MRSA screening by rapid PCR tests

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The control of the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and colonization has become one of the most important issues in hospital settings. Compared with methicillin-sensitive strains, apart from being multi-drug resistant limiting the choice of antimicrobial agents, MRSA colonized patients more frequently develop symptomatic infections. Higher mortality is seen with MRSA bacteraemia and surgical site infections, and more so if the strain also has reduced susceptibility to vancomycin (VISA). Some studies also found increased length of stay and healthcare costs with MRSA infections. The propensity of MRSA to cause outbreaks in institutions makes it a challenge to the hospital epidemiologist.

In Netherlands, hospitals adopt a 'search and destroy' policy to curb transmission of MRSA[1]. All patients admitted to hospitals and healthcare workers are actively screened for MRSA carriage. Patients who are at high risk of MRSA carriage, such as those with history of MRSA infections, or those coming from countries with high prevalence of MRSA infections, are pre-emptively isolated until screening results turn negative. Those screened positive are given decolonization therapy and those with active MRSA infections are treated with standard therapy. With this strategy the prevalence of MRSA is less than 1%. In contrast, in countries where MRSA is prevalent such as United States, the guidelines propose routine implementation of contact precautions to patient who are known to have colonization or infection of MRSA[2][3]. Active screening is recommended in situations when the prevalence of MRSA did not decrease despite routine measures and only in exceptional circumstances such as during outbreaks. Nevertheless, legislative mandates on universal MRSA screening have been introduced in several US states. As in the United States, MRSA is endemic at high levels in Hong Kong. In a local study, the carriage rate on entry to intensive care units was 12.1%[4]. Hospitals adopt a similar approach to USA[5] and emphasize on isolation and cohorting of patients harbouring multi-drug resistant organisms rather than active surveillance.

Recent advances in MRSA screening have enabled shorter turnaround time and early control measures. These include commercially available agar containing chromogenic enzyme substrates. Results could be available in 1 to 2 days. An even more attractive option is by the use of real time polymerase chain reaction (PCR), which produces results in 1 to 2 hours. It has a good sensitivity (86-100%) and specificity (90- 99%). The increased cost of rapid PCR test is a concern. Previous epidemiological and cohort studies found the use of these rapid tests beneficial in some high risk groups, such as before cardiothoracic[6] or general surgical procedures[7], or in intensive care unit settings[8], but insignificant results were noted in others[9].

Several large studies on the use of rapid PCR test for active screening in hospital

settings have recently been published to address this issue. One observational study[10] compared the rates of hospital acquired MRSA infection between a baseline year, a second year when screening was done in intensive care units only and a third year when universal screening was done. Nasal swab of the patients were taken and real time PCR for MRSA was performed, followed by contact isolation if screening was positive. The prevalence densities of hospital-associated MRSA infection expressed in number of infections per 10,000 inpatient days were 8.9 in the baseline period, 7.4 in the intensive care unit-only period (p=15 compared with baseline period), and 3.9 in universal screening period (p< 0.001 compared with baseline period). The methicillin-sensitive *Staphylococcus aureus* bacteraemia rates did not change significantly throughout the 3 periods. The authors concluded that universal admission surveillance was associated with a large reduction for MRSA disease during admission and within 30 days after discharge.

However, this study was limited by the lack of a concomitant control group. Several co-interventions were implemented in the universal screening period, such as ongoing feedback to optimize adherence, and topical decolonization therapy, making direct comparison of the usefulness of the screening test alone impossible. This study did demonstrate that rapid screening test, coupled with appropriate follow-up intervention, was able to reduce MRSA infections.

Another study[11] targeted on the effect of active surveillance in surgical patients. This prospective cohort study was carried out in 12 surgical wards including different subspecialties in a teaching hospital in Switzerland. 6 wards were assigned to the intervention group where patients were screened before or on admission by rapid PCR tests for 9 months. In the other 6 control wards, no screening was done. The 2 groups crossed over for another 9 months after the first period ended. MRSA colonizers were put on contact isolation and decolonization therapy. Prophylactic antibiotics for patient undergoing surgeries were adjusted according to the rapid test results. Out of the 10193 patient screened, 515 (5.1%) were found to be carriers by screening. 93 patients in the intervention period versus 76 patients in the control period developed nosocomial MRSA infections (1.11 and 0.91 per 1000 patient days respectively, p=0.29). Despite control measures, the rates of MRSA surgical site infection and nosocomial MRSA acquisition did not alter significantly. 53 of 93 patients developed nosocomial MRSA infections in spite of negative carriage status on admission. The authors concluded that a universal, rapid MRSA screening strategy did not reduce nosocomial MRSA infection in a surgical department with endemic MRSA but low infection rates.

One limitation of this study was incomplete detection and isolation of MRSA colonizers. Screening was not done after admission and on discharge, and MRSA carriers acquired after hospitalization eluded isolation and added to the spread. Furthermore, this study was unable to identify enough MRSA colonizers to assess the effectiveness of active surveillance to guide preoperative antimicrobial prophylaxis and decolonization on rates of surgical site infection.

A third study[12] paralleled the use of rapid PCR test to conventional culture on MRSA acquisition rates. 10 general wards (including medical, surgical, elderly care, and oncology wards) were randomized to rapid screening or conventional culture group, and patients admitted to these wards were screened before admission, on admission and before discharge. MRSA control measures undertaken included contact isolation, topical decolonization therapy, and pre-emptive isolation of high-risk patients until the status was confirmed negative. After the first intervention period of five months, the wards swapped to the other method in a

second intervention period of five months. Out of the 9608 patients admitted, 8374 were screened negative on admission. There was a reduction in mean reporting time with the use of rapid PCR test compared to conventional culture (46 hours and 22 hours respectively, p< 0.001) and a reduction in inappropriate pre-emptive isolation days with rapid testing (399 days and 277 days respectively, p< 0.001). But there was no significant difference in MRSA acquisition rate (3.2% in conventional culture group and 2.8% in rapid testing group, p=0.61), nor there was significant reduction in MRSA transmission or infection rates between the two groups. The authors concluded that MRSA rapid testing led to quick receipt of results and had an impact on bed usage but did not reduce MRSA acquisition. An MRSA outbreak occurred in both study arms. The low adherence to pre-emptive isolation (33%) and hand washing (47%) may account for this. Moreover, the good negative predictive value of 99.4% of the rapid PCR test was offset by a low positive predictive value of 55.1% only in this study population with a MRSA carriage rate of 6.7%. Thus a proportion of colonizers might have been missed and contributed to nosocomial transmission.

These three studies provide conflicting results, which could be explained by the difference in the study design and outcomes measured. The results of the studies should be interpreted in light of these differences and may not be extrapolated to the local situation. Moreover, the success of a screening programme relies on the efficacy of the control measures, including meticulous hand hygiene, environmental cleansing and disinfection, contact isolation and cohorting of patients, dedicated use of medical equipment, decolonization regimes, judicious use of antibiotics, and staff education.

Hand hygiene has been considered as a cornerstone in preventing the nosocomial transmission of disease. Many retrospective or observational studies could be found in the literature showing reduced nosocomial infection (including MRSA infection rates) with hand hygiene practices. Systemic reviews, however, found lack of rigorous evidence on reduced healthcare infection rates with hand hygiene interventions, as the evidence was based mostly on retrospective studies or before and after studies with methodological flaws and confounding factors[17-19]. One review on the impact of hand hygiene in intensive care units also demonstrated that hand hygiene can decrease the level of contamination by at most 40% and could not eliminate health-care associated infections completely even in ideal settings[18]
.
Environmental cleansing is another approach to reduce health-care associated infections. Heavy environmental contamination had been demonstrated during outbreaks of MRSA infections, but was rarely implicated as the cause of nosocomial transmission. Articles evaluating the usefulness of environmental cleansing are largely expert opinions, case series and a few cohort studies, and these did not show reduced infections rates with routine disinfection as opposed to cleaning with detergent[20]. CDC guideline on environmental infection control recommends the use of standard cleaning and disinfection protocols to control environmental contamination due to antibiotic resistant gram-positive cocci such as MRSA, paying special attention to high-touched items in patient-care area [21].

Contact isolation and cohorting of patients were associated with reduction in nosocomial MRSA colonization and infection rates in some observational studies, whereas systemic reviews could not draw conclusions to recommend practice due to lack of good quality studies[13][14] Short-term use of decolonization therapy may have a role in specific patient groups [16], but systemic review found insufficient evidence to

support routine use of topical or systemic antimicrobial therapy to eradicate MRSA colonization [15]. Emergence of resistance leading to treatment failure has also been reported.

Despite discouraging results of these systemic reviews and lack of well-controlled studies of good quality, successful reduction or even eradication of MRSA infections with persistent and concerted effort of multiple infection control interventions have been reported, in special units such as NICU[22], in hospitals[23] or even in national level as in Scandinavian countries.

In conclusion, the use of rapid PCR test is associated with decreased turnaround time but increased cost. Local study on efficacy and cost-effectiveness of rapid MRSA screening is lacking. Based on the mixed results of the available studies, whether rapid screening testing should be implemented in a local institution depends on the careful assessment of risk and practicability in individual circumstances. Institutions should emphasize on routine infection control measures in general situations.

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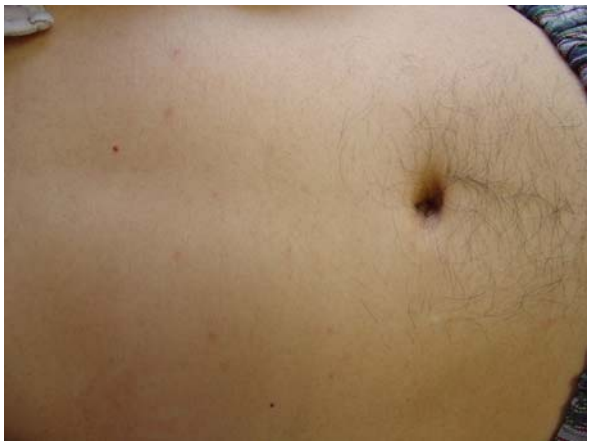
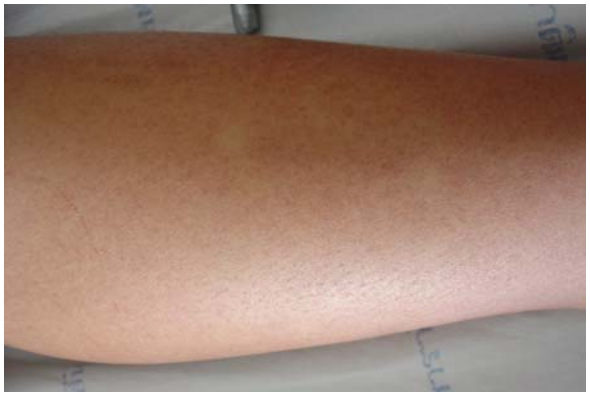
4 short cases with photo quiz

Wilson Lam, Department of Medicine,Queen Elizabeth Hospital



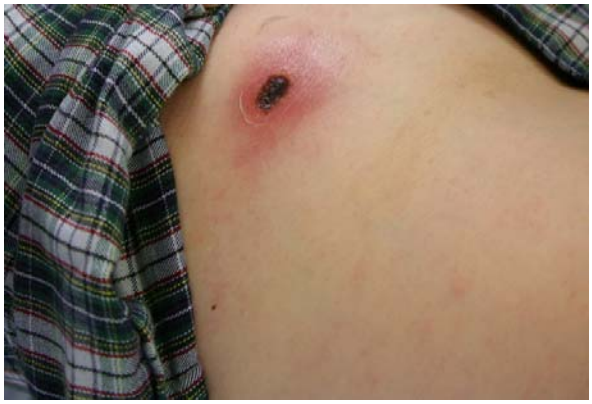
Q: What was the name of the skin rash shown in this patient who presented with fever and Gram-negative bacilli bacteraemia?

A: Rose spots. Salmonella paratyphi A was grown from the blood culture of this patient. Rose spots are small (1-3mm) pink papular lesions in crops of 10-20 on lower chest and upper abdomen. They usually appear 7 to 10 days after fever onset[1] and said to be present in much greater numbers in paratyphoid fever when compared to typhoid[2].



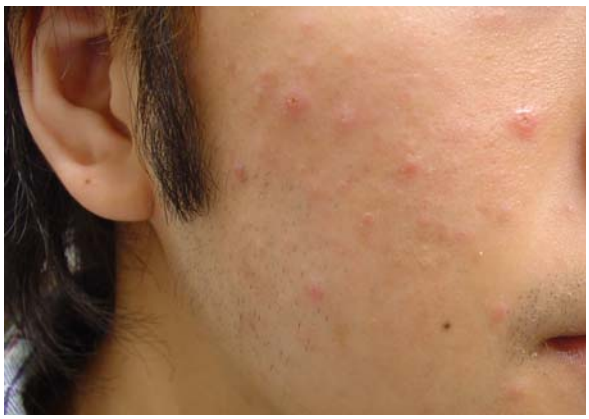
Q: What was the cause of the rash in the leg of this young lady who presented with fever and thromobocytopenia?

A: Dengue fever. The characteristic exanthem of dengue fever includes an initial flushing erythema of the face, neck and chest within the first 24 to 48 hours resulting from capillary dilatation. The subsequent rash, seen 3 to 5 days later, is characterized by a generalized morbilliform eruption with petechiae and islands of sparing [3] (“white islands in a sea of red”, thought to be immune response to the virus, as shown in the picture).



Q: What was the diagnosis of this lady who recently went for hiking presenting with fever and a skin lesion beneath the right breast?

A: Rickettsioses. Characteristic eschar and pale macular rash on the trunk were noted in this patient who had likely contracted the disease in the countryside. Typical eschar is a slightly raised erythema with a black necrotic center. They are the sites of mites or ticks attachment and are found most frequently in warm and damp areas on the body.[4]



Q: What was the cause of the skin lesions in this HIV-infected patient who presented with fever and anaemia?

A: Penicilliosis. Fever, malaise and anaemia were the most common clinical presentations in patients infected with *Penicillium marneffei*. The papular skin lesions, predominantly facial, with central umbilication were seen in 28% of the patients with HIV [5].

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Journal Review

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Al-Nassir WN, Sethi AK, Nerandzic MM, et al. Comparison of clinical and microbiological response to treatment of Clostridium difficile-associated disease with metronidazole and vancomycin. Clin Infect Dis. 2008; 47: 56-62.

In recent years, there have been numerous reports in the literature describing the failure of metronidazole as therapy for Clostridium difficile–associated disease (CDAD). This may be partly attributable to low levels of metronidazole achieved in the gastrointestinal tract, as compared to drugs like vancomycin. In a recent report, US researchers have compared the clinical and microbiological responses to treatment with metronidazole and vancomycin in patients with CDAD over a period of 8 months.

34 patients were initially treated with metronidazole. Among these patients, 10 (29%) were switched to vancomycin within the first 10 days because of persistence of symptoms. None of the 18 patients initially treated with vancomycin required switching.

Patients who were initially treated with vancomycin were significantly more likely than to have resolution of diarrhea and to achieve undetectable levels of C. difficile in the stool during the first 5 days of therapy. Although isolates from patients who experienced treatment failure with metronidazole were all susceptible to the drug, no significant decrease in C. difficile concentrations during metronidazole therapy was found.

Points to note: The findings from this observational study suggest that metronidazole is less effective than vancomycin in reducing fecal concentrations of C. difficile early in the course of treatment. Low levels of metronidazole in the gut may have been the cause for some patients' suboptimal response to the drug.

Cardell K, Akerlind B, Sällberg M, et al. Excellent response rate to a double dose of the combined hepatitis a and B vaccine in previous nonresponders to hepatitis B vaccine. J Infect Dis. 2008; 198: 299-304.

Approximately 5% of hepatitis B vaccine recipients do not generate protective levels of antibodies (10 mIU/mL) to hepatitis B surface antigen (anti-HBs) and are classified as nonresponders. Investigators in Sweden recently assessed the effectiveness of the combined hepatitis A/B vaccine in this population. 44 nonresponders and 20 control participants who were not immune to hepatitis B virus (HBV) or hepatitis A virus (HAV) and had never received the hepatitis B vaccine were given 2 mL of combined hepatitis A/B vaccine at 0, 1, and 6 months; serum samples were obtained before and after the doses to assess the antibody response. Among the 44 nonresponders, 42 (95%) showed protective anti-HBs levels after the third hepatitis A/B vaccine doses, whereas all 20 controls attained such immunity. Among the nonresponders, 35 (80%) developed anti-HBs titers >100 IU/mL. The two persistent nonresponders were smokers, and both smoking and high body-mass index were associated with lower anti-HBs levels. All 64 participants developed anti-HAV antibodies.

Points to note: For hepatitis B vaccine nonresponders who are not immune to HAV, the combined hepatitis A/B vaccine seems to be an effective and well-tolerated approach to generating anti-HBs responses. More study is needed to directly compare this strategy with others and to determine what role the hepatitis A immune response plays in inducing the hepatitis B response. It is also not known whether similar benefits would be seen in patients already immune to HAV.

Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008; 47:

364-71.

Rhino-orbital-cerebral mucormycosis (ROCM) is associated with a poor prognosis, with mortality rate of approximately 50%. Amphotericin B (AmB) and its lipid formulations are currently the only antifungals approved for this condition. Based on the results from in-vitro studies, echinocandins have previously been considered to be inactive against the causative agent. Recently, however, it was found that caspofungin, when combined with AmB lipid complex (ABLC), was active in a murine model of disseminated mucormycosis. Based on these results, researchers began to use caspofungin in combination with various formulations of AmB for patients with ROCM. Now, these researchers have retrospectively reviewed cases of ROCM or rhino-orbital mucormycosis at their two medical centers over a period of 12 years, comparing the results using combination therapy with those using AmB alone, both given together with standard surgical debridement. Thirty-seven patients were evaluable 30 days after hospital discharge. All 6 patients (100%) who received combination therapy were alive, compared with 14 of 31 patients (45%) who received AmB alone. When used as monotherapy, ABLC was found to be less effective; nevertheless, the success rate of ABLC plus caspofungin was statistically similar to that of AmB deoxycholate or liposomal AmB and better than ABLC alone.

Points to note: The empirical use of caspofungin combined with AmB was based on sound experimental data. Despite being only an observational study, these results are extremely encouraging, especially for a disease with such grave prognosis. As mucormycosis is an uncommon condition, it is doubtful that a controlled trial comparing this combination with AmB alone could ever be performed. Clinicians treating patients with ROCM should seriously consider the use of combination therapy based on these results