Featured articles

Novel use of hyperbaric oxygen treatment for treatment-resistant disseminated *Saksenaea* and *Fusarium* in a patient on extracorporeal membrane oxygenation (ECMO): a case report

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Keywords
Case reports; Infection; Mucormycosis; Vaso-invasive fungal disease; Trauma

Abstract

(Devaney B, Mathew J, Ferris S, Roberts L, Covelli C, Orosz J, Nanjayya VB, Fuller A, Millar I. Novel use of hyperbaric oxygen treatment for treatment-resistant disseminated *Saksenaea* and *Fusarium* in a patient on extracorporeal membrane oxygenation (ECMO): a case report. Diving and Hyperbaric Medicine. 2025 December 20;55(4):309–314. doi: 10.28920/dhm55.4.309-314. PMID: 41364853.)

Filamentous soil moulds such as *Saksenaea* and *Fusarium* are angioinvasive fungi responsible for severe disseminated infections. *Saksenaea* causes zygomycosis, with disseminated cases having over ninety percent mortality. *Fusarium*, a hyphomycetes mould, can also cause disseminated infections in immunocompromised individuals, with high mortality. We describe the case of a normally healthy 20-year-old male who survived major traumatic injuries resulting from an aviation incident. He subsequently developed disseminated cutaneous zygomycetes *(Saksenaea)* and *Fusarium* infection with associated immunosuppression, multiorgan dysfunction and sepsis. Treatment strategies included repeated and extensive surgical debridement (inferior orbital region to carotid sheath in the neck, to a depth of buccal mucosa and zygomatic bone in the cheek), antifungal agents including intravenous (IV) liposomal amphotericin B and voriconazole, and IV immunoglobulin and granulocyte colony stimulating factor. Despite maximal medical and surgical treatment, disease control was not achieved. After multi-specialty consensus that current management had failed to control the disease process, hyperbaric oxygen treatment (HBOT) was added to standard therapy on an experimental basis based on several case reports, pathophysiological rationale, and institutional experience with angioinvasive *Mucor*. The patient was on venovenous extracorporeal membrane oxygenation for all HBOT sessions; details are reported separately. Thirteen treatment sessions (243 kPa [2.4 atmospheres absolute], 95 min) were successfully delivered. Local and systemic disease control was achieved within several days of commencing HBOT, and after a prolonged period of rehabilitation and reconstruction, the patient was discharged home. We conclude that HBOT may have an important role in the management of angioinvasive fungal disease.

Introduction

Angioinvasive mould infections usually occur in immunosuppressed patients, or after major trauma. Filamentous hyphae invade and obstruct small blood vessels leading to downstream tissue hypoxia, lactic acidosis and tissue death. Hyperbaric oxygen treatment (HBOT) has been postulated to improve survival primarily via restoration

of normoxia to hypoxic tissues; restoring host immunity, improving viability of marginal tissues and penetration of antifungal therapies, and by stimulating the bone marrow.[1]

We report a case of severe refractory fungal infection with an extremely poor prognosis in which infection control was associated with undertaking HBOT.

Case report

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

We present the case of a healthy 20-year-old male non-Australian citizen who was involved in a military aviation incident in dense tropical bushland in the Northern Territory of Australia. His initial vital signs after being extricated from the immediate vicinity of the aircraft were GCS 14–15, heart rate 140·min^{-1}, systolic blood pressure 85 mmHg. The patient developed a left sided tension pneumothorax and respiratory arrest, for which bilateral finger thoracostomies and intercostal drain insertion were performed at the scene. He was intubated at scene and received eight units of packed red blood cells enroute to the receiving hospital. The pre-hospital time was three hours.

The patient's injuries included grade II liver laceration, splenic hilar injury, splenic flexure retroperitoneal haematoma, pancreatic tail bruising, left lung laceration, multiple spinal fractures (C7 vertebral body, T2-4 superior endplate, T8-10, L1-3 left transverse process, left S3 body and sacral ala), left acetabular fracture, bilateral inferior scapula fractures, 9th–11th left posterior rib fractures, right medial epicondylar avulsion fracture, small subarachnoid haemorrhage, left posterior thigh and gluteal haematoma and penile shaft and scrotal bruising.

In the operating theatre at the receiving hospital, damage control resuscitation and surgery was undertaken including laparotomy, thoracotomy, splenectomy and liver packing. During the left lateral thoracotomy a left pneumonectomy was performed due to uncontrollable hilar bleeding. A brief period of pulseless electrical activity cardiac arrest occurred intra-operatively, requiring internal cardiac massage.

The patient remained severely hypoxic (SaO_2 80–85%) despite FiO_2 1.0, inhaled nitric oxide (20 ppm) and prone mechanical ventilation in the first 24 hours of admission. He was vasoplegic and required high doses of vasopressors (noradrenaline 140 mcg·min^{-1}, vasopressin 3 U·min^{-1}). The extracorporeal membrane oxygenation (ECMO) outreach and retrieval service from our institution was mobilised to the receiving trauma hospital and he was commenced on venovenous (VV) ECMO for ongoing refractory hypoxaemia. A patent foramen ovale was noted during cannulation. He was transferred over 3,000 km by air to our centre on VV ECMO. He remained severely vasoplegic and went on to develop the following complications of his injuries: right renal infarcts and anuric acute kidney injury (managed with continuous renal replacement therapy); cardiac contusion (peak troponin 3,600 ng·L^{-1}); left sided infected haemothorax with radiological evidence of tension and haemodynamic instability (requiring multiple relook thoracotomies for bleeding, washouts of infected collections in the left chest, and left pneumonectomy stump revision); embolic infarcts of the right middle and posterior cerebral arteries and posterior inferior cerebellar artery (with resolution on later imaging); digital ischaemia of his right thumb and left 2nd and 3rd digits (later resolved with minimal intervention); compartment syndrome of the anterior and lateral compartments of the left leg (requiring fasciotomy); rhabdomyolysis; right cephalic vein deep venous thrombosis (DVT) (treated with low dose heparin); and polymicrobial pneumonia of the remaining lung with *Stenotrophomonas maltophila, Burkholderia territorii*, *Burkholderia cepacia complex* and *Acinetobacter baumanii complex* (treated with meropenem and later cefiderocol and sulfamethoxazole-trimethoprim). The patient developed persistent inflammation, immunosuppression, and catabolism syndrome (PICS).[2]

A minor penetrating cheek wound had been noted and irrigated on arrival at our centre. On Day 10 after the initial injury, the surrounding area became erythematous, and the patient developed signs of sepsis and profound sepsis-related lymphopenia. He was taken to theatre for a wash-out of the wound. Biopsy results showed angioinvasive fungal infection, which raised suspicion for mucormycosis. He was found to have disseminated disease with distant infection of the left leg and chest wall.

Two angioinvasive fungal organisms were confirmed: *Fusarium neocosmosporiellum* and *Saksenaea vasiformis* both of which are filamentous soil moulds (Figures 1, 2). Two other soil moulds of uncertain significance, *Curvularia species* and *Pseudothielavia subhyaloderma,* were grown from a forearm wound and the chest wound respectively. The infection progressed locally and systemically. The patient was increasingly septic and underwent multiple, extensive, right facial debridements, including a right radical parotidectomy with complete facial nerve sacrifice (Figures 3, 4). Despite maximal surgical debridement, anti-fungal agents (intravenous liposomal amphotericin B and voriconazole), granulocyte colony stimulating factor (G-CSF) and intravenous (IV) immunoglobulin, fungal invasion continued to progress. Further surgical efforts were discontinued once debridement depth extended to buccal mucosa, to zygomatic, maxillary and mandibular bone in the cheek and fungal growth was found to have invaded the right carotid sheath, threatening the carotid artery. It should be noted that despite repeated up-titration of the voriconazole dose, serum levels remained sub-therapeutic due to sequestration within the ECMO circuit.

At this stage, a multidisciplinary team of US and Australian clinicians considered several treatment options, including

Figure 1
Parotid biopsy with possibly two types of fungi seen (broad hyphae – *Saksenaea*; narrower hyphae invading blood vessel wall – *Fusarium*)

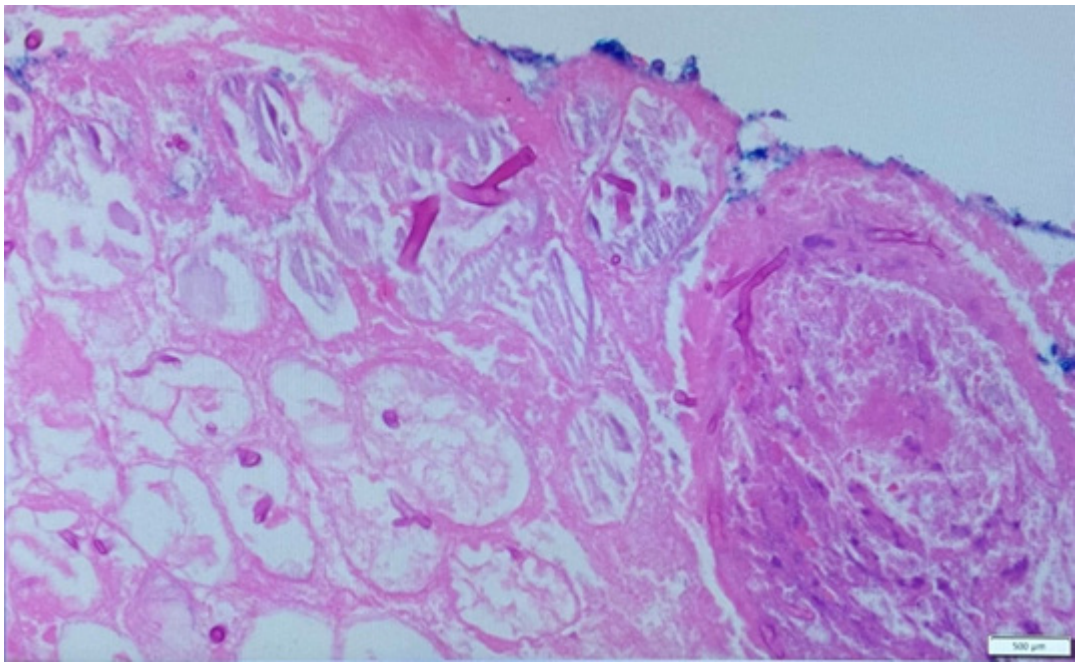
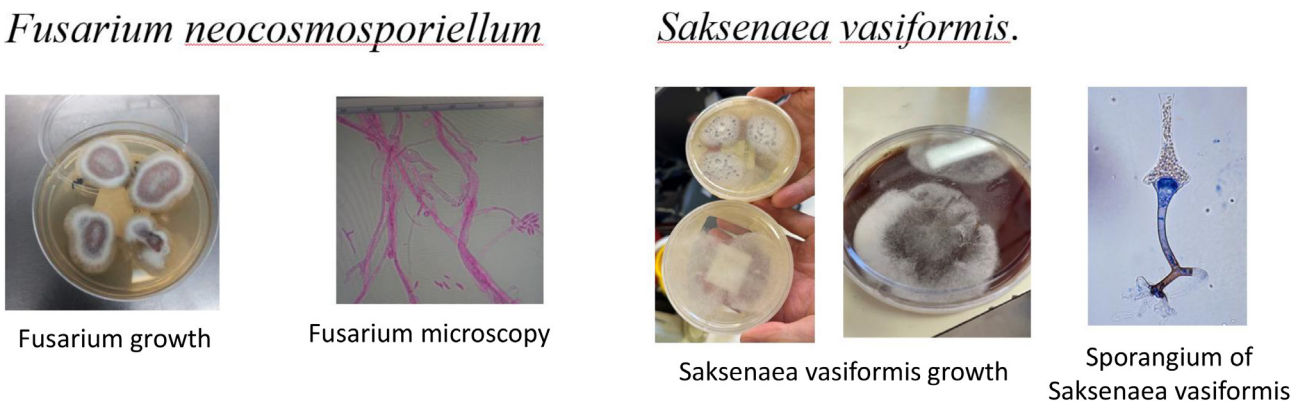


Figure 2
Microbiology plates showing fungal growth and microscopy



total facial debridement followed by a facial transplant, carotid ligation, and flap surgery to enhance circulation to the facial area. However, these options were ruled out after considering the patient's family's wishes, the significant disability, morbidity, and deformity associated with these procedures, and the patient's own preferences regarding quality of life as advised by his family. This decision prompted the exploration of experimental therapies. Based on attractive pathophysiological mechanisms, positive anecdotal and institutional experience with HBOT for advanced *Mucor*, and several published case reports, a decision was made to pursue HBOT as a 'last resort' experimental therapy. A further review in the operating theatre was performed prior to commencing HBOT, which demonstrated macroscopic fungal spread beyond the previous margins however this was not debrided (Figure 4).

A validation process had previously commenced for the use of ECMO in hyperbaric conditions, and is detailed elsewhere.[3,4] Importantly, the device was determined to be safe and to not pose a fire or safety risk to infrastructure or staff. After an expedited planning process, emergency ethics review and clinical innovations committee approval for the inaugural clinical use of ECMO in the hyperbaric chamber, HBOT was commenced daily and in total the patient received 13 treatment sessions over 15 days. Each treatment lasted 95 minutes at a treatment pressure of 243 kPa (2.4 atmospheres absolute). On surgical review after four hyperbaric treatments, the wound bed was noted to be sloughy with no frank mould, and on subsequent reviews the wound became clean and granulating (Figure 5). No significant further surgical debridement was required. Serum voriconazole

Figure 3
Clinical photography: first debridement once microbiology known; seven days prior to commencing hyperbaric oxygen treatment

Figure 4
Clinical photography: day of commencement of hyperbaric oxygen treatment

Figure 5
Clinical photography after completion of hyperbaric treatments

did not reach therapeutic levels prior to cessation of HBOT. The patient's lymphopenia resolved and was replaced by leucocytosis coinciding with reduced requirement for vasopressor support. Due to recurrent mucous plugging of the bronchus to the single remaining lung, the patient was kept on VV ECMO as a safety precaution whilst he was subsequently repatriated to his home country.

After an extensive hospital stay complicated by low-grade empyema, and profound weight loss requiring significant physical therapy and nutritional supports, the patient was decannulated from VV ECMO after approximately three months. Wound cultures and biopsies were negative for fungal disease, and his facial wounds healed with grafting. He was discharged home to the community.

Discussion

Within four days of commencing HBOT for disseminated *Saksenaea* and *Fusarium* in this patient, the previously extensive and progressive fungal growth (which was not able to be acceptably debrided and was left in-situ during the 'final' re-look surgery) had macroscopically resolved. This corresponded with clinical improvement and reduced requirement for haemodynamic support. Complete resolution of fungal disease was later demonstrated by negative wound swab and biopsy cultures.

As the patient was on ECMO when he developed angioinvasive fungal disease, and ECMO had not previously been validated for hyperbaric use, HBOT was only considered when consensus from all treating teams was that current treatment had failed to gain disease control. In this context, the resolution of fungal invasion within days of commencing HBOT makes a convincing case for the role HBOT played in controlling the disease process. Additionally, resolution of fungal invasion in the absence of therapeutic serum voriconazole levels, further underscores the potential significance of the role of HBOT.

The pathogenesis of zygomycosis involves rapid angioinvasion with resultant thrombus formation leading to localised tissue hypoxia and subsequent ischaemia.[5,6] Tissue necrosis limits the ability of the host immune system to deliver leucocytes and anti-fungal agents to the foci of infection and reduces the oxygen carrying capacity of infected tissues. Phagocytic leucocyte function is highly dependent on adequate oxygenation to tissues as leucocytes rely on oxidative radicals to kill invading pathogens and the rate of radical production is directly related to the oxygen tension of the local environment. Hypoxic

(below 30 mmHg) or anoxic environments result in loss of function and killing ability of the leucocytes.[7] Angioinvasive properties of these organisms allow dissemination to other organs. Disseminated disease, such as described in this report, has been reported to have mortality rates approaching 96%.[5,8]

Current mainstays of treatment for zygomycosis include urgent and aggressive surgical debridement and concomitant medical therapy.[9] The combination of surgical management and anti-fungal therapy has been associated with decreased mortality rates. In a review of 693 cases of cutaneous mucormycosis (of which only 13% had disseminated disease), Skiada et al., found that combined therapy had a lower mortality rate (29.6%) compared to medical management alone (36%) or surgical management alone (46.2%).[10] However, mortality remains high, necessitating the introduction of adjuvant therapies. There is limited high quality data to demonstrate the efficacy of HBOT but several case reports and case series describe positive outcomes amongst patients who received HBOT.[11–15]

There are several mechanisms by which HBOT may exert beneficial effects in the management of zygomycosis. HBOT involves the patient breathing 100% oxygen in a pressurised hyperbaric chamber. Treatment pressures are generally 203–304 kPa (2–3 atmospheres absolute); assuming normal gas transfer at the lungs this allows the partial pressure of oxygen in the arterial blood to reach up to ~2,000 mmHg. By accentuating the oxygen gradient between blood and tissue, the diffusion distance of oxygen is increased, and tissue hypoxia can be reversed. Reversal of tissue hypoxia and therefore acidosis, helps maintain local tissue survival.[7,16] Correcting acidosis within the tissues has the added benefit in zygomycoses of potentiating the oxidative action of Amphotericin B.[1,11,17] Periods of restoration of normoxia help combat the thrombotic and ischaemic effects of angioinvasive fungal infections, likely significantly boosting the anti-microbial capacity of leucocytes in the region of the infection.[1,17] Hyperbaric hyperoxia also improves tissue healing by restoring normal fibroblast function, increasing collagen deposition, promoting the secretion of inflammatory cytokines and, after repeated exposure, promoting angiogenesis.[1,18] Hyperoxia has been shown to have direct fungicidal effects on Zygomycetes, with *in-vitro* testing demonstrating complete inhibition of Zygomycetes growth at 24- and 72-h when exposed to 100% O_2 at 203 or 304 kPa (2 or 3 atmospheres absolute).[16]

This patient had two different moulds grown from his tissue samples: *Saksenaea vasiformis,* a Zygomycetes *and Fusarium.* Zygomycotic infections are a life-threatening group of diseases caused by moulds belonging to the class Zygomycetes and orders Mucorales and Entomophtorales.[6,19] The infections may occur in cutaneous, rhino-orbital-cerebral, pulmonary, gastrointestinal, renal or uncommon sites, each with associated risk factors and complications.[8] This report describes the use of HBOT in the management of disseminated skin and soft tissue mucormycosis and *Fusarium* infection resistant to standard management.

Fusarium exhibits resistance to a number of azoles and echinocandins but remains susceptible to natamycin, amphotericin B, voriconazole and posaconazole.[20] In resistant cases, a combination of antifungal drugs should be considered as this increases the efficacy and spectrum of action.[20] Surgical debridement and granulocyte colony stimulating factor have been used in the management of *Fusarium* with resection of all infected tissues recommended.[20] From the searches conducted, there appear to be no reports on the use of HBOT for *Fusarium*, however we suspected that HBOT may play a similar role in the management of *Fusarium* as has been reported in the management of other zygomycosis.

Given the patient was unable to be weaned from VV ECMO prior to HBOT and that validation processes for the Rotaflow Series I ECMO console with PLS1 circuit (Maquet, Rastatt, Germany) and Quadrax-i oxygenator was still underway at our centre, express ethics, clinical innovations committee and executive approvals were sought before proceeding with treatment. The technical details relating to validation of the device, and the governance and workflow procedures utilised to safely deliver VV-ECMO in the hyperbaric chamber are detailed in separate manuscripts.[3,4]

Conclusions

We report a rare case of disseminated cutaneous Zygomycetes (*Saksenaea*) and *Fusarium* in a previously healthy young adult male with severe trauma and associated multiorgan dysfunction, sepsis and immunosuppression. This case indicates that HBOT may rapidly interrupt progression of angioinvasive fungal disease, even in advanced stages. We hypothesise that the primary mechanism involved is the restoration of normoxia (or even hyperoxia) in areas made hypoxic by angioinvasion of fungal hyphae, enabling resumption of oxygen-dependant phagocytic functions. We suggest that clinicians should consider the use of HBOT as an additional treatment modality for angioinvasive fungal diseases such as those caused by Zygomycetes (*Saksenaea*) and *Fusarium,* even, in the right setting, for those requiring VV-ECMO.

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Acknowledgements

We would like to acknowledge the expertise and exceptional efforts of the very large team of Alfred Health personnel who enabled and supported the efforts necessary for success; Executive, Governance committees, Hyperbaric, Intensive Care, Trauma, multiple surgical teams, the Infectious Diseases team; and the US military ECMO and retrieval teams.

Conflicts of interest and funding: nil

Submitted: 17 July 2025
Accepted after revision: 5 October 2025