Although therapeutic opportunities in medicine continuously improve, death is inevitable in some cases due to limitations in treatment. When patients die without a conclusive diagnosis, autopsy studies can provide essential information in order to improve pathophysiological reasoning. We describe two patients who died after a prolonged course of sepsis and were diagnosed with the unsuspected presence of aspergillosis at autopsy. Literature review demonstrates that due to apoptosis and immunological interactions, septic patients become susceptible to opportunistic infections, a state described as immunoparalysis.

Keywords
Aspergillosis, immunosuppression, sepsis, T cell differentiation

Introduction
Sepsis embodies a cascade of systemic inflammatory responses that may progress to severe sepsis and septic shock. It is one of the leading causes of in-hospital death worldwide and represents 11-20% of all intensive care admissions. Mortality increases with severity, and is approximately 46% for patients in septic shock. In the Netherlands, sepsis represents approximately 3500 deaths annually. The Surviving Sepsis Campaign has developed a resuscitation and management bundle in order to standardise patient care in the initial hours after admission. National and international studies have demonstrated that implementation of these bundles significantly reduces mortality. However, even when optimal support is provided, mortality remains relatively high.
growth of *Aspergillus* species, Galactomannan enzyme immunoassay was not performed. The patient’s condition did not improve and leakage of pancreatic secretion caused recurrent gastrointestinal blood loss. CT scan of the thorax revealed atelectasis of the left lower lobe with mild pleural effusion and persistent abdominal fluid collections. Despite repetitive surgical interventions and extensive antibiotic and antifungal treatment, the patient remained septic and eventually died due to multiple organ dysfunction. Autopsy revealed the unsuspected presence of aspergilloma in the respiratory tract with systemic activity and metastatic growth in the heart and kidneys (figure 1).

Two years earlier, a 52-year-old patient with no relevant medical history had developed a similar course after surgical resection of a perforated ileum. Postoperatively, she remained dependent on ventilatory and haemodynamic support. Multiple surgical interventions were performed in order to correct anastomotic leakage, but septic shock persisted. Blood cultures revealed sequential growth of *Pseudomonas aeruginosa*, *Enterococcus faecium* and *Candida albicans*. Thoracic CT scan showed ground glass opacity in the basal fields bilaterally and cystic bronchiectasis in the right lower lobe. As in the case above, *Aspergillus fumigatus* was grown once in the sputum but Galactomannan enzyme immunoassay was not performed. Eventually, the patient developed a severe encephalopathy and although extensive antibiotic treatment was administered, she remained in a depressed state of consciousness. CT cerebrum suggested haemorrhagic lesions in the frontal lobe (figure 2). Consecutive electroencephalography did not reveal improvement in cerebral performance and therefore multidisciplinary consultation concluded to discontinue supportive treatment. At autopsy, vaso-invasive growth of *Aspergillus* was found bilaterally in the lungs, with systemic mycotic emboli and metastatic involvement of the cerebrum.

**DISCUSSION**

As these two cases evidently demonstrate, opportunistic infections may develop in critically ill patients with no history of immune suppression. Invasive aspergillosis is a life-threatening infection that primarily affects patients with haematological malignancies, autoimmune diseases, AIDS or immunosuppressive therapy. Diagnosis is difficult to obtain, since it requires presence of *Aspergillus* in the histopathological analysis of sterile tissue specimens. In the last decade, several case series have described invasive aspergillosis in intensive care patients without a history of immune suppression. As these two cases evidently demonstrate, opportunistic infections may develop in critically ill patients with no history of immune suppression. Invasive aspergillosis is a life-threatening infection that primarily affects patients with haematological malignancies, autoimmune diseases, AIDS or immunosuppressive therapy. Diagnosis is difficult to obtain, since it requires presence of *Aspergillus* in the histopathological analysis of sterile tissue specimens. In the last decade, several case series have described invasive aspergillosis in intensive care patients without a history of immune suppression. As these two cases evidently demonstrate, opportunistic infections may develop in critically ill patients with no history of immune suppression. Invasive aspergillosis is a life-threatening infection that primarily affects patients with haematological malignancies, autoimmune diseases, AIDS or immunosuppressive therapy. Diagnosis is difficult to obtain, since it requires presence of *Aspergillus* in the histopathological analysis of sterile tissue specimens. In the last decade, several case series have described invasive aspergillosis in intensive care patients without a history of immune suppression. As these two cases evidently demonstrate, opportunistic infections may develop in critically ill patients with no history of immune suppression. Invasive aspergillosis is a life-threatening infection that primarily affects patients with haematological malignancies, autoimmune diseases, AIDS or immunosuppressive therapy. Diagnosis is difficult to obtain, since it requires presence of *Aspergillus* in the histopathological analysis of sterile tissue specimens. In the last decade, several case series have described invasive aspergillosis in intensive care patients without a history of immune suppression.
Since the cellular immune system is crucial for protection against opportunistic infections, patients become less competent in eliminating these opportunists. Lastly, the presence of apoptotic cells seems to accelerate lymphocyte tolerance to pathogens, a mechanism described as anergy. The combination of these pathways causes cellular immune system paralysis.

In conclusion, the cascade of sepsis does not end at the stage of septic shock. Immune responses in sepsis are biphasic; the initial hyper-inflammatory phase is followed by anti-inflammatory reactions that induce immunoparalysis. During sepsis, patients with prior normal immune system functioning become susceptible to opportunistic infections such as invasive aspergillosis. This may partially explain the mortality that persists despite the implementation of the Surviving Sepsis Guidelines. Further insight into the immunological disturbances in septic patients may lead to the development of immunomodulatory therapy. Currently, several potentially beneficial immunosupportive agents are being studied in clinical trials.

**REFERENCES**