We report a clinical case of meningoencephalitis with subdural empyema in an immunocompromised farmer caused by toxigenic *Clostridium perfringens* type A, which was identified by 16S RNA gene analysis of cerebrospinal fluid and subdural empyema. In immunocompromised patients, *C. perfringens* should be considered a potential pathogen of sepsis.
incubation. Therefore, biochemical tests and susceptibility testing were not possible. According to MIC data for *C. perfringens* and clinical breakpoints of European Committee for Antimicrobial Susceptibility Testing (EUCAST) for Gram-positive anaerobes (20, 32), antibiotic treatment was adapted to intravenous penicillin (4 million IU 4 times per day [q.i.d.]) and metronidazole (500 mg 3 times per day [t.i.d.]). The disease course was complicated by severe septic shock with multiorgan failure consisting of disseminated intravascular coagulation (DIC) with IVD-associated intracerebral hemorrhage in the left frontal lobe (Fig. 1d), acute respiratory and renal failure, hepatic dysfunction, and aggravated pancytopenia. Intensive care management with mechanical ventilation, hemofiltration, extensive substitution of blood products, and high-dose catecholamine treatment was needed. After stabilization of septic shock, tracheal aspergillosis was microbiologically and histologically diagnosed by biopsy of the tracheal wall and was treated with voriconazole. The patient could be discharged from the ICU after 1 month of intensive care treatment. He remained in a stable condition, and neurologically, continuous improvement of alertness and communication was observed. Spontaneous directed movement of the left hemibody with only slight impairment of force further proved the functional recovery of the right hemisphere. Unfortunately, right-sided hemiplegia caused by the IVD-associated intracerebral hemorrhage in the left frontal lobe (Fig. 1b) did not improve. Four months after the diagnosis of *C. perfringens* type A infection, the patient again developed an SIRS. Due to the poor prognosis associated with unclassified MDS, no further clinical workup was initiated, and he died a few days later. Autopsy revealed subacute myocardial infarction and pneumonia as the direct causes of death. Neuropathological findings confirmed healing subdural empyema with a hemorrhagic component and yellow-stained leptomeninges on the right side consistent with prior CNS infection with *C. perfringens* type A.

The most frequent clinical manifestation of *C. perfringens* infection is myonecrosis, or gas gangrene. If only minor amounts of toxins are produced, infections may present as a mild, self-limiting disease. If local infections spread via hematogenous dissemination, every organ might be involved, including the brain. Central nervous system manifestation of *C. perfringens* infection in humans is rare (9). Most commonly, the meninges are affected (1, 3, 6, 7, 10–14, 16–19, 21, 22, 23–25, 29, 30) after clinical manifestations of sepsis (31). Rarely, focal or diffuse encephalitis with or without pneumocephalus has been presented (2, 13, 22, 27, 29), and only a single case of subdural empyema has been reported in the current literature (23). In our patient due to the clinical findings of generalized epileptic seizure, radiological evidence of progressive brain edema, and detection of *C. perfringens* type A by molecular analysis of CSF and subdural empyema, we diagnosed a meningoencephalitis and subdural empyema with *C. perfringens*. We were unable to cultivate *C. perfringens*, probably due to the antibiotic treatment started 3 days before sampling. However, the diagnosis was unambiguous according to (i) direct microscopic detection of plump Gram-positive, rod-shaped bacteria in large quantities in two independent samples of the subdural lesion and (ii) 100% identification of the 16S rRNA gene PCR amplicon with *C. perfringens* in both clinical samples (cerebrospinal fluid and subdural empyema). In addition, the *cpa* gene, which codes for the virulence factor alpha-toxin of *C. perfringens* type A, was amplified and confirmed by sequence analysis.

Usually, infections with *C. perfringens* start from a recent surgical wound, trauma, or intra-abdominal disease, such as infections of the biliary tract or other gastrointestinal infections (26). However, in most of the cases of *C. perfringens* meningoitis, the site of infectious origin remains unidentified (6, 11, 13, 14, 18, 21, 23, 24, 28), as in our patient. *C. perfringens* is a common part of the intestinal flora of domestic animals, such as cattle, and the bacteria are spread into the environment by feces (33). In our case, gastrointestinal disease caused by a food-borne infection was ruled out. There was a history of minor trauma caused by a strike of a cow’s hoof 3 weeks before onset of symptoms. Possibly, *C. perfringens* type A was carried on the cow’s hoof and transmitted into the wound. Due to the preexisting coagulopathy and the history of trauma, we assume a chronic subdural hematoma as the site of onset for the CNS manifestation. Although repeated normal aerobic and anaerobic blood cultures remained negative, a transient bacteremia with *C. perfringens* type A is likely to have happened in a chronically exposed and immunocompromised farmer.

Subdural empyema and diffuse encephalitis with *C. perfringens* are reported to be fulminant and have a fatal outcome in 30 to...
100% of untreated patients (9). The functional recovery in our patient might be explained by the early targeted therapy with penicillin and metronidazole. There are expert recommendations but no in vivo data regarding the treatment of C. perfringens CNS manifestations (21). In vitro, antibiotic drugs with activity against Gram-positive anaerobic bacteria (penicillin, clindamycin, and metronidazole) reportedly show low MICs (32). To date, no C. perfringens isolates resistant to penicillin, clindamycin, or metronidazole according to EUCAST clinical breakpoints for anaerobic Gram-positive rods (20) have been described. In the treatment of a brain abscess with C. perfringens, a favorable outcome after immediate surgical debridement or drainage was reported (5, 8).

In conclusion, we report the first case of cerebral infection due to C. perfringens type A manifested with subdural empyema and diffuse meningoencephalitis, which was diagnosed by 16S rRNA sequencing and a multiplex PCR approach. The patient was successfully treated with targeted antibiotic therapy and surgical removal of subdural empyma. Even though rarely reported, C. perfringens type A should be considered a differential pathogen in a patient with immunosuppression. If no pathogen can be cultivated due to ongoing antibiotic treatment, molecular analysis such as broad-range 16S RNA PCR is a valuable and rapid tool leading to an accurate diagnosis.

Nucleotide sequence accession number. The 16S sequence of the patient’s isolate has been submitted to GenBank under accession no. JQ782390.

REFERENCES