# Nosocomial Infections in the Neurointensive Care Unit

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**KEYWORDS**

• Nosocomial infections • Hospital-acquired pneumonia • Ventriculitis
• Urinary tract infection • EVD-related infection

**KEY POINTS**

- Nosocomial infections in the neurointensive care unit (neuro-ICU) are common, with varying incidences for the different disease groups, with pneumonia being the most common infection.
- Nosocomial meningitis and ventriculitis are a specific problem for the neuro-ICU population, largely linked to craniotomy and placement of central nervous system devices.
- Brain-immune interactions become dysregulated after acute brain injury, with autonomic shift to enhanced sympathetic response and multiple modifications of the immune system leading to increased susceptibility to infections.

## INTRODUCTION

Infectious complications occur in up to 36% of patients admitted to the neurointensive care unit (neuro-ICU) for more than 48 hours.[1] Most common are pneumonia, urinary tract infections (UTIs), bloodstream infections, and intracranial infections (meningitis and ventriculitis).[2] Ventilator-associated pneumonia (VAP), defined as pneumonia in patients undergoing mechanical ventilation for at least 48 hours,[3] develops because of aspiration of contaminated oropharyngeal secretions around the endotracheal cuff.[3] Nosocomial infections in general are a major threat to critically ill patients, contributing to increased mortality, worse functional outcomes, a higher cost of health care, with increased use of medical resources and increased hospital readmission rates.[4–9] Nosocomial pneumonia is associated with prolonged length of stay (LOS) and increased in-hospital death among intensive care unit (ICU) patients,[10–12] and sepsis and VAP are major causes of death during ICU hospitalization of brain-injured patients.[13]

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Identified general risk factors for nosocomial infections include prolonged LOS, presence of medical comorbid conditions, use of invasive devices, and use of antibiotics.[14] Furthermore, poor hand hygiene has been shown to be one of the most important causes of health care–associated infections.[15] In mixed ICU populations, reported rates for pneumonia are 5% to 47%,[16,17] UTI 7% to 27%,[2,18] meningitis and ventriculitis 1% to 20%,[2,19,20] and bacteremia 1% to 2%.[2,19]

The neuro-ICU population poses a specific challenge in the diagnosis of infections: the occurrence of fever may not be infectious but a manifestation of the brain injury. In severely brain-injured patients, the incidence of fever in the first week of hospitalization has been as 87%.[21] In a prospective study of fever in neurocritical care patients in whom fever occurred in about 25% of patients, almost half were noninfectious.[22]

## BRAIN INJURY–INDUCED IMMUNE DYSREGULATION

Why are patients with acute brain injury so susceptible to infections? It has long been recognized that acute brain injury results in a considerable inflammatory response that includes both peripheral and central production of proinflammatory cytokines, chemokines, and cell adhesion molecules.[23,24] Although inflammatory response is necessary to clear cellular debris in the central nervous system (CNS) after injury and for reparative functions,[25] prolonged, chronic inflammation is postulated to be deleterious.[26–28] Over recent years, evidence has accumulated from animal models as well as research in humans that brain-immune interactions become dysregulated after acute brain injury and ischemia, resulting in a so-called brain injury–induced immunosuppression syndrome.[29] Although most data stem from studies in ischemic stroke, the systemic immunodepression is not unique to ischemic stroke and can also follow any other brain injury, including traumatic events, brain surgery, subarachnoid hemorrhage, or spinal cord injury.[30,31] This response of the immune system to acute brain injury is biphasic and occurs as soon as 12 hours after stroke, with early transient activation lasting up to 24 hours,[32,33] followed by systemic immunodepression that can persist for several weeks.[31,32] It is triggered by an intense activation of the hypothalamic-pituitary axis and the sympathetic nervous system with subsequent release of catecholamines,[34–36] and is mediated through β2-adrenergic receptors.[37] Enhanced sympathetic activity with high catecholamine levels and subsequent suppressed immune function has been firmly associated with the occurrence of poststroke infections.[38–40]

How does the immune modulation occur? The primary neurotransmitter of the sympathetic nervous system, norepinephrine, is released into the lymphoid tissue and modulates the function of immune cells.[41] Multiple modifications of the immune response have been described in response to this sympathetic activation, including lymphocyte depletion and increased lymphocyte apoptosis, impaired function of monocytes with decreased HLA-DR (human leukocyte antigen, antigen D related) expression, and reduced NK-cell activity.[34,36,40] Furthermore, a shift from T-helper (Th) 1 to Th2 cytokine production,[35,36,42] increased release of inflammatory cytokines from activated T cells,[33] a higher CD4/CD8 T-cell ratio, and enhanced production of tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) by blood and spleen lymphocytes[32] have been shown, and large numbers of platelets are released from the spleen following sympathetic stimulation.[43] The resultant immune depression has largely been attributed to an increase in number of systemic regulatory T cells,[32,33] reduced IFN-γ production, as well as impaired natural killer (NK) and T-cell response with insufficient activation of phagocytic cells at the site of infection.[36,44]