Review

Nosocomial infections and immunity: lesson from brain-injured patients

Tomasz Dziedzic, Agnieszka Slowik and Andrzej Szczudlik

Department of Neurology, Jagiellonian University, Krakow, Poland

Corresponding author: Tomasz Dziedzic, dziedzictom@mediclub.pl or Dziedzic@neuro.cm-uj.krakow.pl

Published online: 19 February 2004
This article is online at http://ccforum.com/content/8/4/266

Critical Care 2004, **8:**266-270 (DOI 10.1186/cc2828)

Abstract

Of brain-injured patients admitted to intensive care units, a significant number acquires nosocomial infections. Increased susceptibility to infectious agents could, at least partly, be due to transient immunodepression triggered by brain damage. Immune deficiency in patients with severe brain injury primarily involves T cell dysfunction. However, humoral and phagocytic deficiencies are also detectable. Activation of the hypothalamo–pituitary–adrenal axis and the sympathetic nervous system plays a crucial role in brain-mediated immunodepression. In this review we discuss the role of immunodepression in the development of nosocomial infections and clinical trials on immunomodulation in brain-injured patients with hospital-acquired infections.

Keywords brain injury, immunodepression, infection, intensive care

Introduction

An infection that is not present or incubating when a patient is admitted to hospital but is detected 48–72 hours after admission is considered to a nosocomial rather than community-acquired infection [1]. Nosocomial infections affect about 30% of patients in intensive care units (ICUs; incidence rates range between 9% and 37%, depending on the population studied and the definition used) [2]. Patients with severe brain injury appear to be at greater risk for nosocomial infections than other ICU patients. In one study [3], 41 out of 82 (50%) patients with severe head injury experienced at least one infectious complication during their hospitalization. Piek and coworkers [4] examined 734 patients with severe head trauma and identified pulmonary infections in 41% and septicaemia in 10% of patients. Fassbender and colleagues found that 1 week after admission to hospital 27% of 52 patients with ischaemic stroke fulfilled criteria for hospital-acquired infection [5]. Hilker and coworkers [6] prospectively evaluated 124 patients with acute stroke who were treated at a neurological ICU. In that study the incidence of stroke-associated pneumonia was 21%. Berrouane and colleagues [7] found higher incidence rates of early-onset pneumonia in patients with neurotrauma than in patients without neurotrauma hospitalized in a neurosurgical ICU (20.1/1000 versus 15.7/1000 patient days and 34.2/1000 versus 27.9/100 ventilation days). Ventilator-associated pneumonia is among the most important subtypes of nosocomial infections, and the incidence of this type of pneumonia in brain-injured patients ranges from 28% to 40% [8].

Development of nosocomial infection depends on two key factors: decreased host defences and colonization by pathogenic micro-organisms. Here, we review the significance of immune status in development of nosocomial infections in brain-injured patients. Mechanical causes of immunodepression (e.g. intubation and invasive procedures) are not discussed here. Data for the review were identified by searches of the Medline database, the Cochrane Library and references from relevant articles (January 1980 to June 2003). Search terms included the following: 'head trauma', 'brain injury', 'infection', 'immunity' and 'intensive care'.

CARS = compensatory anti-inflammatory response syndrome; G-CSF = granulocyte colony stimulating factor; ICU = intensive care unit; IVIG = intravenous immunoglobulin; IL = interleukin; IFN = interferon; TNF = tumour necrosis factor.

Table 1

Immunological defects in brain-injured patients

Defect	Examples
T cells	Reduced number of total circulating T cells, T-helper cells, T-suppressor cells, natural killer cells and IL-2 receptor-bearing cells [11–15]
	Disproportionate high percentage of T cells of the $CD4^+/CD45^+$ (suppressor/inducer) phenotype relative to the percentage of T cells of the $CD4^+/CDw29^+$ (helper/inducer) phenotype [16]
	Reduction in the proliferative response of T cells to mitogen stimulation [11–14]
	Decreased IFN-γ and IL-2 production [13,17]
	Anergy to delayed-type hypersensitivity skin testing [11–13]
	Depression in lymphokine-activated killer cell cytotoxicity [13,17]
B cells [14,15]	Reduction in IgG and IgM
	Reduction in components of complement system (C1q, C2, properdin)
Neutrophils [15,18]	Decrease in superoxide generation
Monocytes [19–21]	Increased IL-6 and IL-10 production

IFN, interferon; IL, interleukin.

Why are infections so frequent in brain-injured patients – is 'immunoparalysis' involved?

Immune deterioration has been reported in patients after trauma, surgery, or blood loss (for review [9,10]). Alterations in host defence mechanisms after trauma that are potentially important to development of infectious complications include the following: paralysis of monocyte function (transient nonreactivity of monocytes toward stimulation with endotoxin, depression of antigen presentation capacity, and enhanced secretion of the anti-inflammatory cytokine IL-10); suppression of T cell functions (decreased response to mitogenic activation and decreased IL-2 production); and impairment of B-cell function (decreased capacity to produce antibodies).

The high frequency of infection in brain-injured patients suggests that host defences may be compromised after severe brain trauma, even in the absence of clinically important systemic injury. In the early 1990s several groups showed independently that severe brain injury precipitates significant deficiencies in the immune system, and this finding was confirmed and later extended by other researchers. Immunological abnormalities that are found in patients with brain injury are summarized in Table 1 [11–21].

The cellular arm of immunity is the most affected, although phagocytic and humoral deficiencies are also detectable. Defects in cellular immunity include reduced number of circulating T cells, increased proportion of suppressor cells, depressed mitogen-induced proliferative response, and depressed delayed-type hypersensitivity reaction [11–16]. Moreover, it has been postulated that monocytes could be target cells in brain-mediated immunosuppression; monocyte deactivation, with decreased capacity for antigen presentation and depressed secretion of proinflammatory cytokines, increased the risk for infectious complications [21].

Immunodeficiencies are noted soon after brain injury; for example, T-cell anergy is seen within several hours after brain damage [12]. These deficiencies are most prominent during the first few days after brain injury [14,17] and precede the infectious complications, which reach a peak incidence at 5–11 days after brain trauma [4]. The immunodepression in brain-injured patients appears to be a transient phenomenon. Recovery of T-cell function was observed 3 months after head injury [14]. In patients with a vegetative state, all neutrophil functions (superoxide release, migration and chemotactic capability) were found to be normal when measured several months after the brain damage [18]. Further studies are needed to determine how the immune system recovers after brain damage and to compare the recovery process between brain-injured and other ICU patients.

The mechanisms that lead to immunological defects in patients with head trauma or severe stroke are still poorly understood. In many cases immune deficiencies (defect in cellular immunity, monocyte deactivation) closely resemble those observed in patients after 'non-neurological' trauma, surgical injury, or blood loss [10]. Generally, local infection or sterile trauma induces a local inflammatory response, with release of proinflammatory mediators (tumour necrosis factor [TNF]-α, IL-1β, IL-6). Overwhelming immune activation can result in systemic inflammatory response syndrome and septic shock. To control the potentially harmful proinflammatory response, the immune system releases several anti-inflammatory mediators (IL-10, IL-1 receptor antagonist, soluble TNF-α receptor), causing compensatory anti-inflammatory response syndrome (CARS). Monocyte deactivation with decreased capacity for antigen presentation and depressed secretion of proinflammatory cytokines appear to be critical events in CARS.

Cerebral insults can also cause a brain-mediated systemic anti-inflammatory syndrome [22]. Brain cytokines triggered by trauma, ischaemia, or haemorrhage can activate CARS, even in the absence of preceding systemic inflammation. Both locally produced cytokines in the brain and direct brain-stem irritation can trigger strong sympathetic activation and stimulation of the hypothalamo–pituitary–adrenocortical axis [22]. Glucocorticoids possess anti-inflammatory and immunosuppressive properties. They inhibit synthesis of proinflammatory cytokines (IL-1, TNF-α), and can augment the secretion of the anti-inflammatory cytokine IL-10 [23]. In addition, glucocorticoids suppress expression of major histocompatibility complex class II molecules on antigen-presenting cells and can inhibit various lymphocyte functions. Catecholamines inhibit TNF-α production by monocytes and increase IL-10 release [24,25].

It should be also kept in mind that some drugs used in the ICU can impair immune responses. These include glucocorticoids, catecholamines, benzodiazepines [26], midazolam and propofol [27]. On the other hand, the histamine-2 receptor antagonist ranitidine can modulate immune response by increasing interferon (IFN)-γ production by lymphocytes [28].

Can we effectively prevent and treat nosocomial infections in brain-injured patients – is there a role for immunomodulatory therapy?

Various immunomodulatory agents, including IFN-γ, granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor and immunoglobulins, have been used in ICU patients to prevent or treat nosocomial infections by activating the immune system. Here we discuss the results of studies focused on brain-injured patients.

G-CSF promotes the differentiation and proliferation of neutrophil precursor cell, prolongs the survival of neutrophils, and acts as a chemoattractant for granulocytes. In a randomized, placebo-controlled, double-blind, multicentre phase II study [29], 40 patients with head trauma were given one or two daily doses of recombinant human G-CSF (filgrastim) for up to 10 days after hospitalization. The primary study end-points were an increase in absolute neutrophil count; frequencies of nosocomial pneumonia, urinary tract infection and primary bacteraemia; and safety of G-CSF. Secondary end-points were serum G-CSF level; duration of hospitalization, antibiotic use and ICU stay; and 28-day survival. Filgrastim caused a dose-dependent increase in absolute neutrophil count. There was no difference in pneumonia and urinary tract infections between groups. The incidence of hospital-acquired bacteraemia was significantly reduced in patients treated with high-dose G-CSF (300 μg/day) compared with those treated with placebo (0/19 [0%] versus 5/17 [29%]). There was no difference between groups in any of the secondary end-points. That study did not address the issue of the possible deleterious effects of G-CSF on the injured brain [30], although this drug appears to be safe for extracerebral complications [31].

In another study [32], administration of recombinant human G-CSF ameliorated life-threatening infections without causing lung injury or brain swelling in patients with severe head injuries who were treated with a combination of high-dose barbiturates and mild hypothermia. In that study eight patients with head trauma received recombinant human G-CSF for 5 days, and the results of treatment were compared with those in 22 patients who were not administered recombinant human G-CSF. In patients treated with recombinant human G-CSF, total leucocyte count, nucleated cell count and neutrophil function increased significantly, whereas levels of C-reactive protein and IL-6 decreased. Seven out of eight patients treated with recombinant human G-CSF recovered from life-threatening infections, and none of the eight patients died. In contrast, in patients who did not receive recombinant human G-CSF, infections continued after 5 days in 17 out of 22 patients, seven of whom died from severe infections during hospitalization.

Intravenous immunoglobulin (IVIG) can modulate the immune response in several ways, including by Fcγ receptor mediated immunomodulation, by its impact on the idiotype/anti-idiotype network, and by elimination of immunostimulating microbial products (e.g. toxins, superantigens) [33]. An analysis of randomized trials conducted by the Cochran Infectious Diseases Group showed that polyclonal IVIG significantly reduced mortality in sepsis and septic shock [34]. Gooding and coworkers [35] conducted a randomized, double-blind trial to determine whether IVIG decreases the incidence of secondary infections in head-injured children. Eighteen children with severe head injury received IVIG (400 mg/kg) and 14 received albumin placebo within 48 hours after admission. Unfortunately, no significant differences in the incidence of pneumonia or in any other type of infection were noted. In addition, there were no differences between groups in the number of days on mechanical ventilation and in the number of hospital days.

The available literature suggests that, in trauma and peri-operative patients, immunonutrition may reduce the number of infectious complications (for review [36]). Enhancing immunity through diet is generally done by adding n-3 fatty acids, arginine and nucleotides to an otherwise nutritionally complete formula. Most trials have unfortunately failed to demonstrate any benefit of such interventions in terms of important outcomes such as mortality [36].

Rapp and coworkers [37] reported the first prospective, randomized trial to suggest that early administration of parenteral nutrition can influence immune status in head-injured patients. In that study patients were randomly assigned to receive parenteral nutrition (20 patients) within 48 hours of admission or nasogastric tube feedings (18

patients). After 18 days of hospitalization, eight out of 18 enteral nutrition patients died whereas no deaths occurred in the patients receiving parenteral nutrition. Reactions to skin test antigens were used throughout the study as a measure of immunological function. Approximately 40% of patients receiving parenteral nutrition exhibited positive skin test reactions, as compared with 14% of patients receiving enteral nutrition ($P < 0.04$).

In another study [38], nine patients with severe closed-head injury were prospectively randomized either to early parenteral nutrition (four patients) at day 1 or to delayed parenteral nutrition (five patients) at day 5. Significant increases in total $CD4^+$ cell counts, a rise in the $CD4^+/CD8^+$ ratio and improved lymphocyte responses after mitogen stimulation were noted in patients receiving early nutrition as compared with those receiving delayed parenteral nutrition.

The results of a systematic review assessing the significance of nutritional support for head-injured patients suggested that early feeding may be associated with a trend toward better outcome in terms of survival and disability, but further studies are needed [39].

Rixen and coworkers [28] demonstrated an immunomodulatory effect of the histamine-2 receptor antagonist ranitidine, both at cellular and mediator levels, in patients after severe head injury. In that randomized, prospective, double-blind study, nine patients received continuous infusion of ranitidine (6.25 mg/hour) for up to 5 days and 11 patients received placebo. Treatment with ranitidine, but not with placebo, was associated with a significant increase in $CD4^+$ lymphocytes, increased IFN-γ production after mitogen stimulation, and significant decrease in $CD8^+$ lymphocytes. The mortality rate was similar between groups; one patient died in placebo group, and among those treated with ranitidine no patients died.

Conclusion

Reports published to date on modulation of immune function in brain-injured patients have several flaws. The number of included patients was too small to draw firm conclusions. Examined groups were heterogeneous with respect to aetiology of brain injury (trauma, haemorrhage) and severity of disease. Although T lymphocytes appear to be the most affected in patients with brain injury, there is a lack of studies attempting to modulate cell-mediated immunity in brain-injured patients.

Several important issues should be addressed in future studies. First, the mechanisms responsible the immunodepression in brain-injured patients (e.g. endocrinological and stress-related mechanisms) require further exploration. Second, future studies should be conducted in large groups of carefully selected patients at high risk for infection. It is important to select appropriate patients for immunotherapy. Patients with severe brain injury are not good candidates for immunotherapy because death in this group is usually not directly related to infectious complications but rather is caused by brain-stem damage. Therefore, in this group potentially beneficial effects of immunotherapy can be overwhelmed by the primary brain damage. Finally, the specific cytokines or growth factors that have the greatest therapeutic impact, and which are the patient populations that will derive the greatest benefit remain to be defined.

Competing interests

None declared.

References

1. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: **CDC definitions for nosocomial infections.** *Am J Infect Control* 1988, **16:**128-140.
2. Vincent JL: **Nosocomial infections in adult intensive-care units.** *Lancet* 2003, **361:**2068-2077.
3. Helling TS, Evans LL, Fowler DL, Hays LV, Kennedy FR: **Infectious complications in patients with severe head injury.** *J Trauma* 1988, **28:**1575-1577.
4. Piek J, Chesnut RM, Marshall LF, van Berkum-Clark M, Klauber MR, Blunt BA, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA: **Extracranial complications of severe head injury.** *J Neurosurg* 1992, **77:**901-907.
5. Fassbender K, Dempfle CE, Mielke O, Rossol S, Schneider S, Dollman M, Hennerici M: **Proinflammatory cytokines: indicators of infection in high-risk patients.** *J Lab Clin Med* 1997, **130:** 535-539.
6. Hilker R, Poetter C, Findeisen N, Dobesky J, Jacobs A, Neveling M, Heiss W-D: **Nosocomial pneumonia after acute stroke. Implications for neurological intensive care medicine.** *Stroke* 2003, **34:**975-981.
7. Berrouane Y, Daudenthun I, Riegel B, Emery MN, Martin G, Krivosic R, Grandbastien B: **Early onset pneumonia in neurosurgical intensive care unit patients.** *J Hosp Infect* 1998, **40:** 275-280.
8. Fabregas N, Torres A: **Pulmonary infection in the brain injured patient.** *Minerva Anestesiol* 2002, **68:**285-290.
9. Angele MK, Faist E: **Clinical review: immunodepression in the surgical patient and increased susceptibility to infection.** *Crit Care* 2002, **6:**298-305.
10. Chaudry IH, Ayala A: **Mechanism of increased susceptibility to infection following hemorrhage.** *Am J Surg* 1993, **165(2A Suppl):**59S-67S.
11. Quattrocchi KB, Frank EH, Miller CH, MacDermott JP, Hein L, Frey L, Wagner FC Jr: **Suppression of cellular immune activity following severe head trauma.** *J Neurotrauma* 1990, **7:**77-87.
12. Hoyt DB, Ozkan AN, Hansbrough JF, Marshall L, vanBerkum-Clark M. **Head injury: an immunological deficit in T-cell activation.** *J Trauma* 1990, **30:**759-766.
13. Miller CH, Quattrocchi KB, Frank EH, Issel BW, Wagner FC Jr: **Humoral and cellular immunity following severe head injury: review and current investigations.** *Neurol Res* 1991, **13:**117-124.
14. Meert KL, Long M, Kaplan J, Sarnaik AP: **Alterations in immune function following head injury in children.** *Crit Care Med* 1995, **23:**822-828.
15. Wolach B, Sazbon L, Gavrieli R, Broda A, Schlesinger M: **Early immunological defects in comatose patients after acute brain injury.** *J Neurosurg* 2001, **94:**706-711.
16. Quattrocchi KB, Miller CH, Wagner FC Jr, DeNardo SJ, DeNardo GL, Ovodov K, Frank EH: **Cell-mediated immunity in severely head-injured patients: the role of suppressor lymphocytes and serum factor.** *J Neurosurg* 1992, **77:**694-699.
17. Quattrocchi KB, Frank EH, Miller CH, Amin A, Issel BW, Wagner FC Jr: **Impairment of helper T-cell function and lymphokine-activated killer cytotoxicity following severe head trauma.** *J Neurosurg* 1991, **75:**766-773.
18. Wolach B, Sazbon L, Gavrieli R, Ben-Tovim T, Zagreba F, Schlesinger M: **Some aspects of the humoral and neutrophil**

functions in post-comatose awareness patients. *Brain Inj* 1993, **7:**401-410.
19. Woiciechowsky C, Schoning B, Cobanov J, Lanksch WR, Volk HD, Docke WD: **Early IL-6 plasma concentrations correlate with severity of brain injury and pneumonia in brain-injured patients.** *J Trauma* 2002, **52:**339-345.
20. Dziedzic T, Bartus S, Klimkowicz A, Motyl M, Slowik A, Szczudlik A: **Intracerebral hemorrhage triggers interleukin-6 and interleukin-10 release in blood.** *Stroke* 2002, **33:**2334-2335.
21. Shimonkevitz R, Bar-Or D, Harris L, Dole K, McLaughlin L, Yukl R: **Transient monocyte release of interleukin-10 in response to traumatic brain injury.** *Shock* 1999, **12:**10-16.
22. Woiciechowsky C, Schoning B, Lanksch WR, Volk HD, Docke WD: **Mechanisms of brain-mediated systemic anti-inflammatory syndrome causing immunodepression.** *J Mol Med* 1999, **77:**769-780.
23. Wiegers GJ, Reul MHM: **Induction of cytokine receptors by glucocorticoids: functional and pathological significance.** *Trends Pharmacol Sci* 1998, **19:**317-321.
24. Severn A, Rapson NT, Hunter CA, Liew FY: **Regulation of tumor necrosis factor production by adrenaline and beta-adrenergic agonists.** *J Immunol* 1992, **148:**3441-3445.
25. van der Poll T, Coyle SM, Barbosa K, Braxton CC, Lowry SF: **Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia.** *J Clin Invest* 1996, **97:**713-719.
26. Taupin V, Jayais P, Descamps-Latcha B: **Benzodiazepine anesthesia in humans modulates the interleukin-1 beta, tumor necrosis factor-alpha and interleukin-6 responses of blood monocytes.** *J Neuroimmunol* 1991, **35:**13-19.
27. Galley HF, Dubbels AM, Webster NR: **The effect of midazolam and propofol on interleukin-8 from human polymorphonuclear leukocytes.** *Anesth Analg* 1998, **86:**1289-1293.
28. Rixen D, Livingston DH, Loder P, Denny TN: **Ranitidine improves lymphocyte function after severe head injury: results of a randomized, double-blind study.** *Crit Care Med* 1996, **24:**1787-1792.
29. Heard SO, Fink MP, Gamelli RL, Solomkin JS, Joshi M, Trask AL, Fabian TC, Hudson LD, Gerold KB, Logan ED: **Effect of prophylactic administration of recombinant human granulocyte colony-stimulating factor (filgrastim) on the frequency of nosocomial infections in patients with acute traumatic brain injury or cerebral hemorrhage.** *Crit Care Med* 1998, **26:**748-754.
30. Whalen MJ, Carlos TM, Clark RSB, Kochanek PM: **An acute inflammatory response to the use of granulocyte colony-stimulating factor to prevent infections in patients with brain injury. What about the brain?** *Crit Care Med* 1999, **27:**1014-1018.
31. Pettila V, Takkunen O, Varpula T, Markkola A, Porkka K, Valtonen V: **Safety of granulocyte colony-stimulating factor (filgrastim) in intubated patients in the intensive care unit: interim analysis of a prospective, placebo-controlled, double-blind study.** *Crit Care Med* 2000, **28:**3620-3625.
32. Ishikawa K, Tanaka H, Takaoka M, Ogura H, Shiozaki T, Hosotsubo H, Shimazu T, Yoshioka T, Sugimoto H: **Granulocyte colony-stimulating factor ameliorates life-threatening infections after combined therapy with barbiturates and mild hypothermia in patients with severe head injuries.** *J Trauma* 1999, **46:**999-1007.
33. Volk HD: **Immunoglobulins: possible mechanisms of action in autoimmunity and inflammation.** In: *Immunomodulation with Immunoglobulins for Autoimmune Diseases and Infections*. Edited by Kiehl MG, Nass WP, Volk HD. Sttutgart, New York: Thieme; 2000:1-5.
34. Alejandria MM, Lansang MA, Dans LF, Mantaring JBV: **Intravenous immunoglobulin for treating sepsis and septic shock [Cochrane review].** In: *The Cochrane Library*, Issue 3. Oxford: Update Software; 2003.
35. Gooding AM, Bastian JF, Peterson BM, Wilson NW: **Safety and efficacy of intravenous immunoglobulin prophylaxis in pediatric head trauma patients: a double-blind controlled trial.** *J Crit Care* 1993, **8:**212-216.
36. McCowen KC, Bistrian BR: **Immunonutrition: problematic or problem solving?** *Am J Clin Nutr* 2003, **77:**764-770.
37. Rapp RP, Young B, Twyman D, Bivins BA, Haack D, Tibbs PA, Bean JR: **The favorable effect of early parenteral feeding on survival in head-injured patients.** *J Neurosurg* 1983, **58:**906-912.
38. Sacks GS, Brown RO, Teague D, Dickerson RN, Tolley EA, Kudsk KA: **Early nutrition support modifies immune function in patients sustaining severe head injury.** *J Parenter Enteral Nutr* 1995, **19:**387-392.
39. Yanagawa T, Bunn F, Roberts I, Wentz R, Pierro A: **Nutritional support for head-injured patients.** *Cochran Database Syst Rev* 2002, **3:**CD001530.