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Stroke-induced immunosuppression and poststroke infection

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ABSTRACT

Infections occur commonly after stroke and are strongly associated with an unfavourable functional outcome of these patients. Approaches for effective management of poststroke infection remain scarce, presenting an urgent need for preventive anti-infection strategies for patients who have suffered a stroke. Emerging evidence indicates that stroke impairs systemic immune responses and increases the susceptibility to infections, suggesting that the modification of impaired immune defence could be beneficial. In this review, we summarised previous attempts to prevent poststroke infections using prophylactic antibiotics and the current understanding of stroke-induced immunosuppression. Further elucidation of the immune mechanisms of stroke will pave the way to tailored design of new treatment to combat poststroke infection via modifying the immune system.

INTRODUCTION

Infectious complications, pneumonia, urinary tract infections and infections in other organ systems, are common in patients with stroke with an incidence of ~30%.[1–3] Poststroke infection is associated with about 20% of the deaths and related to considerable morbidity in stroke survivors.[1 4–6] Given the well known detrimental effects of stroke-associated infection, effective management is critical. Antibiotics are the traditional approach used to manage infections, however, the recently completed clinical trials haven't demonstrated significant benefit of prophylactic antibiotics,[7–10] presenting an urgent need to better understand the pathogenesis of stroke-associated infection and identify viable approaches to combat infectious complications. The inhibition of immunity after stroke has been recognised as a key contributor to infection in patients with stroke. Our increasing knowledge on stroke-induced immunosuppression poses an opportunity to boost immune defence and restrict poststroke infection. In this review, by summarising previous studies regarding attempts to manage poststroke infections and mechanisms of stroke-induced immunosuppression, we aim to provide insight into the basis of stroke-induced immunosuppression and propose new modalities to restore host immune defence after stroke.

Prophylactic antibiotic treatment

Studies in animal models of ischaemic stroke have demonstrated that preventive treatment with antibiotics reduces the incidence of infections, and improves mortality and neurological function.[9] Based on these encouraging findings, a series of clinical trials that tested the safety and efficacy of prophylactic use of antibiotics in patients with stroke have been conducted (table 1). Among these 15 clinical studies, patient inclusion, stroke types, antibiotics selection and treatment duration differ from each other. The majority of these studies treated patients with broad-spectrum antibiotics to cover the most common causative bacteria of pneumonia and urinary tract infections, except for three studies that tested the neuroprotective effects of minocycline, which has inadequate bacterial coverage for patients with stroke; the infection results were not reported in these studies as well.[11–13] A meta-analysis of a portion of these studies concluded that preventive treatment with antibiotics could reduce infection rates, but failed to reduce mortality and improve functional outcomes.[14] This observation resembles findings in two recently completed phase III trials.[7 8] Results from the Preventive Antibiotics in Stroke Study (PASS), which included 2358 patients from 30 Dutch centres, show that preventive antibiotic treatment after stroke was able to reduce poststroke infections, but did not improve functional outcomes at 3 months.[8] The other phase III trial, testing prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF), enrolled 1217 patients from 48 stroke units in the UK; it reported that prophylactic antibiotics did not reduce the frequency of pneumonia within 14 days after stroke onset, either as defined by algorithm or diagnosed by a physician. The secondary end point analyses showed that prophylactic antibiotics did not improve functional recovery at 3 months or mortality.[7]

Although the PASS and STROKE-IFN studies are different in many aspects, such as treatment time window, antibiotics selection

Table 1 Clinical studies of antibiotic treatment in patients with stroke

Study	Design	Stroke type	Sample size	Antibiotics regimen	Primary outcomes	Conclusion on patients' outcome	Conclusion on infection
Halms *et al*[61]	Phase 2, randomised, double-blind, placebo controlled	Ischaemic	79	Moxifloxacin, 400 mg daily for 5 days starting within 36 hours	Infection within 11 days	Improved neurological outcome and survival.	Reduced infection.
Chamorro *et al*[62]	Phase 2, randomised, double-blind, placebo-controlled	Ischaemic/haemorrhagic (110/26)	136	Levofloxacin, 500 mg daily for 3 days, starting within 24 hours	Incidence of infection 7 days after stroke	Levofloxacin could lessen the chances of functional recovery.	Did not prevent infection.
Schwarz *et al*[63]	Phase 2, randomised, controlled	Ischaemic	60	Mezlocillin plus sulbactam, 2 g/1 g every 8 hours for 4 days, starting within 24 hours	Incidence and height of fever	May be associated with a better clinical outcome.	Decreased infection.
Amiri-Nikpour *et al*[11]	Phase 2, open-label, evaluator-blinded	Ischaemic	53	Minocycline 200 mg daily for 5 days, starting from 6 hours to 24 hours	NIHSS score at 90 days	Better outcomes at 90 days in the minocycline group.	NA
Kohler *et al*[13]	Phase 2, randomised open-label, blinded end point evaluation	Ischaemic/haemorrhagic (77/11)	95	Minocycline 100 mg every 12 hours, five doses in total, within 24 hours	mRS at 90 days	Safe but not efficacious.	NA
Lampl *et al*[12]	Phase 2, open-label, evaluator-blinded	Ischaemic	152	Minocycline 200 mg daily for 5 days, starting within 6–24 hours	NIHSS change from baseline to 90 days	Improved patients' outcome at 90 days.	NA
Ulm *et al*[15]	Phase 2, randomised, controlled	Ischaemic	197	PCTus-guided antibiotic, starting within 40 hours for 7 days	mRS at 3 months	Did not improve functional outcome at 3 months.	Did not reduce pneumonia.
Westendorp *et al*[8]	Phase 3, randomised, open-label, masked	Ischaemic/haemorrhagic (2125/269)	2538	ceftriaxone 2 g, intravenously once daily for 4 days starting within 24 hours after onset	mRS at 3 months	Did not improve functional outcome at 3 months	Reduced all infection rates and urinary tract infection rates, but not pneumonia.
Kalra *et al*[7]	Phase 3, cluster-randomised, open-label, masked	Ischaemic/haemorrhagic (1091/125)	1217	Antibiotic conformed to local policy, starting within 48 hours, for 7 days	Pneumonia in the first 14 days	Did not improve neurological function and outcome.	Did not reduce pneumonia.

mRS, modified Rankin Scale; NA, not available; NIHSS, National Institute of Health Stroke Scale; PCTus, procalcitonin ultrasensitive.

and patient inclusion criteria, the results of the two studies are highly consistent, that is, the treatment regimens of both studies failed to reduce the rate of pneumonia. Additionally, a recent study which tested antibiotic treatment in patients selected by the ultrasensitive procalcitonin test did not find a reduction of pneumonia in antibiotic-treated patients either.[15] Therefore, since the antibiotic selection and treatment time window in these studies cannot prevent poststroke pneumonia, a possible explanation is that stroke-associated pneumonia might partly be a pneumonitis with more sterile components.[16] In light of this speculation, the pathophysiological changes in the lung poststroke warrant further investigations for possible identification of new treatment strategies.

Although these clinical studies indicated that several antibiotics in different patients with stroke are safe, limitations regarding the selection of antibiotics for patients with stroke were also noted. For example, some antibiotics have neurotoxic effects and can worsen outcome. A preclinical study found that enrofloxacin (a fluoroquinolone antibiotic) treatment from day 1 to day 7 in rats undergoing middle cerebral artery occlusion, an ischaemic stroke model, worsened outcomes at 1 month.[17] In this context, antibiotics that have neuroprotective properties should be considered in priority, like minocycline[12 18] and ceftriaxone.[19] However, the benefit of ceftriaxone was not demonstrated in PASS, which yielded to the secondary consideration of antibiotics choice, that is, whether broad-spectrum antibiotics are suitable for intervention in patients with stroke. Exposure to these broad-spectrum antibiotics may cause dysregulation of normal flora in the body, which might influence the stroke outcome, as suggested by a recent animal study in which broad-spectrum antibiotic treatment caused depletion of mice intestinal flora, worsening the outcome of stroke.[20] Therefore, the selection of antibiotics for patients with stroke must comprehensively consider the benefits as well as secondary adverse effects of the treatment.

As a severe type of stroke, intracerebral haemorrhage (ICH) accounts for about 10%–15% of all stroke types and is associated with high mortality and morbidity.[21 22] Infection is also a common and important complication in patients with ICH, and it can influence neurological function in the acute phase as well as long-term recovery.[5 23] The reported infection rates in patients with ICH are similar to those with acute ischaemic stroke (AIS), about 30% of all patients, with higher rates in more severe patients admitted to an intensive care unit.[24 25] Currently, studies that have specifically tested antibiotic treatment in patients with ICH are still lacking. However, four of the published studies mentioned above (table 1) also recruited patients diagnosed with ICH. Two studies included only 26 and 11 patients with ICH, respectively, and thus are not suitable for subgroup analysis. In PASS, 269 patients with ICH were enrolled; subgroup analysis indicated that preventive ceftriaxone does not improve outcome in these patients either, however, whether or not preventive ceftriaxone was able to reduce the rate of pneumonia post ICH was not reported. In the STROKE-IFN Study, 125 patients with ICH were included; subgroup analysis indicated that prophylactic antibiotic treatment might reduce the rate of pneumonia in patients with ICH within 14 days after stroke, a noteworthy finding that warrants further confirmation in future studies with larger sample sizes.

Overall, for patients with AIS, prophylactic antibiotic treatment can reduce the rates of both total and urinary tract infections, but no such benefit was seen for stroke-associated pneumonia. In addition, preventive antibiotic treatment does not improve the outcome in patients. Hence, these findings do not support the use of antibiotics in a preventive manner. Preclinical and clinical evidence for the use of antibiotics in patients with ICH requires further enlightenment.

Stroke-induced immunosuppression

The immune system and nervous system crosstalk with each other via multiple facets to maintain the homoeostasis of both systems under physiology conditions.[26–30] Severe brain injuries, including stroke, can interrupt such balance and lead to a series of changes in both systems.[31] Brain injury after an ischaemic or haemorrhagic stroke leads to the activation and infiltration of inflammatory cells into the brain.[32–35] While poststroke inflammation may contribute to the clearance of tissue debris and tissue repair, most published literature indicates that inflammation in the brain during the acute phase of stroke promotes the expansion of stroke lesions and worsens neurodeficits.[36–38] Further, inhibition of the immune response in the brain during the acute phase can limit the extent of stroke injury.[33 34 38–42] Conversely, the injured brain can reshape peripheral immunity and transition the functional status of the peripheral immune system from competence to suppression after the acute phase of stroke, as manifested by lymphopenia, decreased levels of inflammatory cytokines, monocyte and lymphocyte dysfunction, and atrophy of secondary lymphoid organs.[31 36 43 44] Brain lesion size has been considered as an independent risk factor of poststroke immunosuppression and infectious complications.[45] It has been postulated that stroke-induced immunosuppression might be an adaptive response to acute brain injury, because systemic immunosuppression may limit the overwhelming inflammation in the brain or reduce the occurrence of autoimmune reactions against neuroantigens.[46 47] However, a protective role of immunosuppression after stroke, if any, is uncertain and remains to be defined.

A consequence of immunosuppression has been linked to the increased risk of infection after stroke onset.[47] An established concept is that brain-derived neurogenic innervations are in control of systemic immunity. In the context of stroke, brain injury-induced activation of neurogenic pathways, including the sympathetic innervation, hypothalamic-pituitary-adrenal (HPA) axis and parasympathetic innervation work together

to influence the magnitude and intensity of systemic immune response.[43 48] The central mediators of these pathways include norepinephrine, acetylcholine and glucocorticoid hormones.[27 31] Receptors of these molecules are broadly expressed in immune cells.[43 49] Activation of the sympathetic nervous system induces the release of catecholamines from sympathetic nerve terminals. Transient increase of catecholamine release often leads to increased blood immune cells by mobilising them from peripheral reservoirs such as the spleen; however, stroke induces a prolonged elevation of circulating catecholamines,[44] which promotes the apoptosis of immune cells and leads to a decrease of peripheral immune cells and a bias towards T helper cell 2 (Th2) immune response.[50 51] Glucocorticoids, key mediators for HPA axis function, have antiproliferative effects to induce apoptosis of immune cells.[52] Additionally, glucocorticoids can promote the production of anti-inflammatory cytokines like transforming growth factor β (TGF-β),[53] while inhibiting the production of proinflammatory cytokines, such as interleukin (IL) 1, IL-8 and umor necrosis factor α (TNF-α).[54] The anti-inflammatory effects of cholinergic pathways mediated by acetylcholine was recently uncovered; macrophages can be quickly inhibited when exposed to acetylcholine, with decreased secretion of proinflammatory cytokines like TNF-α, IL-1β and IL-18.[55]

In addition to peripheral immunosuppression, stroke also suppresses immunity in the ischaemic brain. Ischaemic neurons can secrete several neurotransmitters like acetylcholine (Ach), glutamate, serotonin, and so on, which can directly interact with the receptors of peripheral infiltrated lymphocytes and modulate their functional status.[43] A model of stroke-induced immunosuppression is illustrated in figure 1 using natural killer (NK) cells as an example. The identification of the mechanisms underlying stroke-induced immunosuppression offers the possibility of the use of immune modulation as a novel approach to boost host defence and combat poststroke infections.

Potential therapies to combat stroke-associated infection

Animal experiments demonstrated that pharmacological blockade of the sympathetic pathway or HPA axis by β-blockers or glucocorticoid receptor antagonists could reduce stroke-induced immune dysfunction and poststroke infection to improve animals' functional outcome (table 2).[48 56] However, the clinical relevance remains unclear (table 3). A small prospective study indicated that β-blocker use is associated with less severe stroke at presentation, with lower thrombin, haemoglobin A_1C levels, and erythrocyte sedimentation rate.[57] Another retrospective analysis of 841 patients with ischaemic stroke, 10.6%

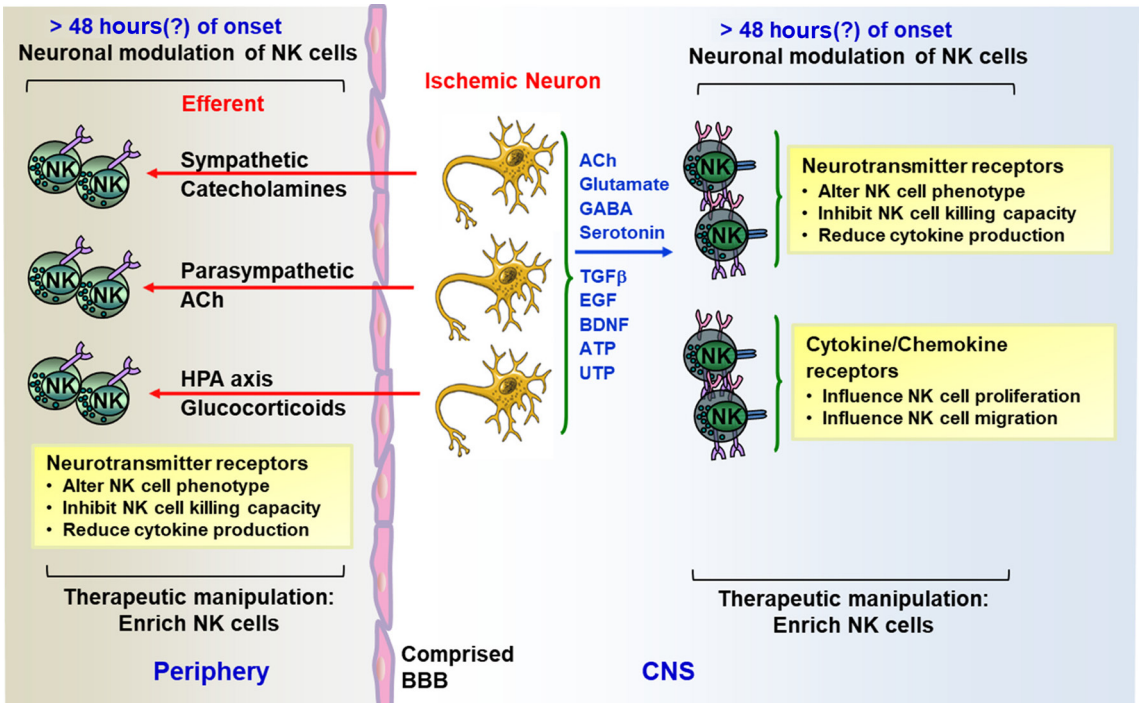

Figure 1 Schematic diagram of mechanisms of stroke-induced immunosuppression with NK cells as an example. In the early stages of stroke (<24 hours), ischaemic neuron-recruited NK cells are swiftly mobilised into ischaemic areas, where they promote neuronal death (not shown in figure).[34] Subsequently (>48 hours?), ischaemic neuron-derived signals can turn off NK cells that express neurotransmitter receptors. At the peripheral level, ischaemic brain injury influences the sympathetic, parasympathetic (vagus nerve) and/or hypothalamic-pituitary-adrenal (HPA) axis systems that suppress NK cell-mediated immunity. Differences in the spectrum of neurogenic innervations, immune cell subsets and soluble mediators in the CNS versus the periphery may differentially affect $_{NK}$ cell deficiency in these two compartments. BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; EGF, epithelial growth factor; GABA, gamma-aminobutyric acid; NK, natural killer; UTP, uridine triphosphate.

Table 2 Preclinical studies regarding neurogenic pathway modulation after stroke

Study	Objects	Approaches	Conclusions
Prass *et al*[56]	Mouse, 60 min MCAO	β-blocker, propranolol	Prevented bacterial infections post-MCAO and reduced mice mortality.
		HPA blocker, RU486	Did not prevent bacterial infections after MCAO.
Mracsko *et al*[64]	Mouse, 60 min MCAO	β2-adrenergic receptor blocker	Preserved IFN-γ production by lymphocytes after stroke.
		HPA blocker, RU486	Prevented poststroke lymphopenia.
Ajmo Jr *et al*[65]	Rat, permanent MCAO	Pan-adrenergic receptor blocker, carvedilol	Prevented the reduction in spleen size, reduced infarct volume; propranolol treatment also had no effects on spleen size and stroke outcome.
		β-blocker, propranolol	No effects on spleen size and stroke outcome.
		α1 receptor blocker, prazosin	Prevented the reduction in spleen size; no effect on infarct volume.
Römer *et al*[46]	Mouse, both WT and 2D2, 60 min MCAO	β-blocker, propranolol HPA blocker, RU486	Both reduced infarct volumes, decreased infection rate and increased long-term survival of 2D2 and WT mice; increased autoreactive CNS antigen-specific T cell responses in the brain but did not worsen functional long-term outcome in the 2D2 stroke model.
Wong *et al*[48]	Mouse, 60 min MCAO	β-blocker, propranolol	Preserved iNKT cell function and reduced poststroke infection.
Liu *et al*[43]	Mouse, 60 min MCAO	β-blocker, propranolol HPA blocker, RU486	Propranolol and RU486 synergistically inhibited immunosuppression poststroke, prevented infection and improved the functional outcome of mice.

2D2 mice, myelin oligodendrocyte glycoprotein (MOG) T cell receptor transgenic mice; HPA, hypothalamic-pituitary-adrenal axis; IFN -γ , interferon-γ; iNKT, invariant NKT; MCAO, middle cerebral artery occlusion; WT, wild type.

of whom received β-blockers during hospitalisation, also implied that β-blockers might be neuroprotective, as the use of β-blockers was associated with reduced risk of early death; however, this association no longer exists when excluding mortality from cardiovascular causes.[58] Of interest, a study that included 625 patients, among which 553 patients were admitted with AIS and 72 with ICH, reported that β-blocker exposure, defined as receiving β-blockers prior to stroke and continued treatment during hospitalisation, did not reduce the risk of stroke-associated pneumonia, but reduced urinary tract infection rates. In addition, patients receiving β-blocker therapy showed a higher 30-day mortality than those without exposure to β-blockers.[59] However, a recent non-randomised study of 5212 patients with ischaemic stroke suggested that, either treatment with β-blockers before stroke onset or starting treatment after stroke onset was associated with reduced frequency of pneumonia, and β-blocker exposure during stroke was associated with reduced mortality.[60] In PASS, 885 patients received β-blockers, but subgroup analysis of this factor was not reported and further analysis regarding the safety and efficacy of such therapy on stroke outcome, as well as in combination with preventive antibiotic treatment, is awaited. Thus, the safety of systemic β-blockade remains controversial in the context of patients with stroke, and randomised trials may be warranted for further determination. In particular, the adverse effects of systemic inhibition of sympathetic input by β-blockers might counteract its protective effect of immune modulation, which warrants further verification. Ultimately, developing selective blockers of lymphocytic β-adrenergic receptors or downstream signalling pathways might avoid the adverse systemic impacts.

Boosting peripheral immunity might serve as another viable approach to countering poststroke infections and avoiding the systemic effects of neurogenic innervations. Preclinical data have demonstrated that adoptive transfer T or NK cells, as well as injection of IFN-γ to animals during the subacute stage of ischaemic stroke (>24 hours) reduces the rate of pneumonia and improves the outcome.[43 56] Additionally, treating animals subjected to brain ischaemia with α-galactosylceramide, a specific activator that can promote proinflammatory cytokines production by the invariant natural killer T cell (NKT) (iNKT) cell, is able to reduce stroke-associated infections.[48] Currently, the safety and efficacy of this approach has not been tested in clinical trials. Nevertheless, before translation to the clinic, the contribution of different cell types and cytokines to restrict stroke-associated infections require further investigations.

CONCLUSIONS

Poststroke infections, especially pneumonia, still present challenges for clinical management of patients with stroke. Preventive administration of antibiotics can somewhat reduce infection rates but not pneumonia, and cannot improve the outcome and survival in patients with stroke; thus, the use of antibiotics in a prophylactic manner remains controversial. Modulation of the

Table 3 Clinical use of β-blockers in patients with stroke

Study	Design	Stroke type	Sample size and group	End points	Conclusions
Raedt *et al*[66]	Subgroup analysis of two lubeluzole studies	Ischaemic	1375, with 264 receiving β-blockers	Poor functional outcome (mRS >3) at 3 months	Use of β-blockers does not appear to influence stroke severity and functional outcome at 3 months.
Laowattana *et al*[57]	Prospective	Ischaemic	111, with 22 treated with β-blockers	Stroke severity on presentation gauged by Canadian Neurologic Scale (CanNS)	Use of β-blocker is associated with less severe stroke on presentation and may be cerebroprotective.
Dziedzic *et al*[58]	Retrospective	Ischaemic	841, with 88 treated with β-blockers	30-day case fatality	β-blocker use was associated with reduced risk of early death.
Maier *et al*[59]	Historical cohort study	Ischaemic/ Haemorrhagic 553/72	625, with 301 treated with β-blockers	Pneumonia, urinary tract infections and death	β-blocker therapy did not reduce the risk for poststroke pneumonia, but significantly reduced the risk for urinary tract infections; patients with β-blocker therapy showed higher 30-day mortality.
Sykora *et al*[60]	Non-randomised	Ischaemic	5212, with 1155 treated with β-blockers before stroke and 244 started in acute phase	Mortality, functional outcome (mRS), occurrence of pneumonia	β-blocker therapy was associated with reduced pneumonia frequency; treatment started in acute phase of stroke was associated with reduced mortality; no association with functional outcome.

mRS, modified Rankin Scale.

immune system via neurogenic pathways may serve as a potential therapy for patients with stroke. Reported clinical studies indicated a discrepancy in the responsiveness to treatment between poststroke pneumonia and other infections, such as urinary tract infection. This suggests that poststroke pneumonia could be more refractory to treatment than other types of infections. Considering the currently limited treatment options for stroke, future design of stroke treatment is imperative to mitigate immunosuppression, and thus to decrease the risk of infectious complications after stroke.

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