

# Systemic infections after acute stroke

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After an acute stroke, systemic infection can complicate the recovery process and lead to a worse clinical outcome, including a higher risk of mortality. Post-stroke infection (PSI) is responsible for the majority of the mortality occurring between 1 week and 1 month after stroke, peaking towards the end of the second week. The effects of PSI on longer-term outcome and other aspects of recovery, such as cognition, mood and quality of life, are largely unknown. The cerebrovascular event itself may result in a systemic immunosuppressed state, hence lowering the threshold for subsequent systemic bacterial infections. Although there have been advances in the basic understanding of the pathophysiological mechanisms of PSI, clinical studies have not provided any clear guidelines on the best methods of managing or preventing PSI. This article provides a review of the current knowledge of the phenomenon of PSI and the possible future developments in the understanding and treatment of PSI.

## Infection & risk of stroke

In the past decade, there has been an increasing understanding in the complexity of the relationship between chronic infection, inflammation, and atherosclerotic diseases, including myocardial infarction and stroke [1,2]. Many studies have demonstrated that serum markers of *Helicobacter pylori*, *Chlamydia pneumoniae*, *Cytomegalovirus* and odontopathogens may predict the future risk of cerebrovascular disease, even after adjusting for traditional risk factors and socio-economic status [3–5]. However, other studies have not found significant associations [6]. The relationship between chronic infection and cardiovascular and cerebrovascular diseases remains controversial and any causal links are far from being proven [7–9]. What is more widely accepted is that markers of inflammation, and in particular C-reactive protein, can independently predict future cardiovascular and cerebrovascular events [10–14].

## Frequency of occurrence of post-stroke infections

After an acute stroke, the patient is at high risk of developing many medical and neurological complications, one of the most common being post-stroke infection (PSI). These complications can seriously prolong and challenge the recovery process as well as increase the risk of mortality and morbidity [15]. In a large, hospital-based German Stroke Databank, the most common serious medical complications in the first week of hospitalization were recurrent stroke and pneumonia [16]. In a large UK-based study,

pneumonia and urinary tract infections (UTIs) were the most frequently observed medical complications [17].

In general, PSIs are found to occur in 25–65% of patients admitted to hospital with acute stroke [15,17–23]. In these studies, pneumonia occurs in 4–22% of all stroke patients, and UTIs occur in 3–44% [15,17–19,21,24–28].

There are many possible reasons for the wide variations in frequencies reported by the observational studies. In particular, investigators have used different methods of patient selection, diagnostic criteria for PSI and duration of observation [29]. Nonseptic fever can sometimes be misinterpreted as PSI (and treated with antibiotics) if physical examination reveals confusing clinical signs and if the necessary investigations are not undertaken to confirm the presence of bacteria.

PSI is associated with significant additional hospital and community costs. The average extra cost of hospitalization was estimated to be US\$ 14,000 higher for patients with post-stroke pneumonia compared with those who did not suffer pneumonia [30]. In this study, patients with post-stroke pneumonia were also 70% more likely to be discharged with requirements for community care, and the cost of this is likely to be very substantial.

## Stroke as a risk factor for developing infection

Although infection is common after stroke, and some studies have found an association between stroke and hospital-acquired infections [31,32],

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there is no clear evidence whether acute stroke *per se* independently increases the risk of systemic infections, or whether the risk is higher purely as a result of the consequences of being acutely unwell (e.g., immobility and poor nutritional state) [33,34]. It is well known that other nonstroke acute medical conditions can also lead to hospital-acquired infections, and studies have reported very wide variations in the frequency of their occurrence, from very low (2–10%) [32,35] to levels found amongst stroke cohorts (~20%) [36].

Whether transient ischemic attack (TIA) increases the risk of PSI is much less clear. In one large prospective study of patients admitted with stroke or TIA, patients with stroke had an 18% risk of developing PSIs within the first week, whereas patients with TIA had a 15% risk of developing PSI [29]. These numbers are, of course, very small and cannot lead to definitive conclusions, but if TIA could also increase the risk of infections, then it is potentially a very interesting finding. In particular, it leads to several hypotheses: a) that an acute cerebrovascular event (whatever the duration) could lead to pathological processes (e.g., immunodeficiency) that may predispose the patient to infections, even though TIA is associated with a significantly shorter duration of neurological deficit; b) the harmful exposure to hospital environment is a much more important contributor to the development of PSI than the severity or duration of neurological symptoms; and c) certain subgroups of patients with TIA may be more susceptible to PSI, for example those with permanent neuronal damage (such as those detectable on diffusion-weighted MRI).

#### Reasons for developing infection after stroke

After an acute stroke (especially with a more severe stroke), the neurological and functional deficits lead to a higher level of dependency, which can potentially predispose a patient to PSI. In one recent study, dysphagia, urinary incontinence (and urinary catheterization) and reduced level of consciousness were found to be predisposing factors for PSI [29]. Dysphagia is known to increase the risk of aspiration pneumonia, dehydration and malnutrition [37–39]. Previous studies have shown that approximately half of all stroke patients with dysphagia will experience aspiration, and over a third of these patients will develop aspiration pneumonia and approximately half will develop malnutrition [37]. A

reduced level of consciousness can further increase the risk of aspiration by downregulating the patient's cough reflex, leading to poor clearance of secretions [40]. Interventions such as nasogastric feeding, which are traditionally regarded as safe methods of providing nutrition for patients at risk of aspiration, have been shown to only provide limited protection against aspiration pneumonia [41].

Urinary incontinence, which is very common after acute stroke, can result in perineal maceration and skin breakdown (and hence cellulitis) [42]. Despite a clear causal link between urinary catheterization and UTI [31], acute stroke patients are still commonly managed using a urinary catheter, especially during the early period [43]. Urinary catheterization not only encourages bacterial growth [44,45], but the formation of a biofilm that forms on the inside of the indwelling catheter also serves to protect the causative bacteria from host defences and antibiotic therapy, hence conveying a survival advantage to the bacteria [31]. In 2007, Kwan *et al.* demonstrated that urinary catheterization increased the odds of developing a post-stroke UTI by three- to four-fold, even after adjusting for case mix [29]. Interestingly, this study also showed that urinary catheterization increased the odds of developing pneumonia after stroke by two- to threefold, but the reasons for this were unclear [29]. Other potential reasons why acute stroke patients can be predisposed to PSI include malnutrition [46], the use of peripheral or central venous catheters, hyperglycemia and prolonged bed-rest.

#### Other risk factors for developing post-stroke infection

Several studies have tried to identify other predictors for PSI [16,24,29,47–51]. In one recent large prospective series, patients who experienced PSI within the first week of admission were on average 5 years older, significantly more dependent before admission, had more severe strokes (40 vs 20% suffering a total anterior circulation stroke), and were more likely to have urinary catheters inserted on admission [29]. Cerebral haemorrhage does not appear to be a significant predictor of PSI. Other studies have also confirmed the association between PSI and markers of stroke severity [24,51], as well as the arterial territory affected by the stroke (e.g., middle cerebral artery territory [49] and brainstem [50]). Speech difficulty, level of disability on admission, and poor mental test scores have been found to independently predict the development of pneumonia after

stroke [52]. High post-voiding residual bladder volume, level of education and level of motor function recovery have also been found to predict the development of UTI after stroke [31].

Several laboratory parameters have been found to be predictors of PSI. In one study, patients with PSI had a significantly higher level of serum urea (an indication of dehydration), and a lower platelet count [29]. In another study, lower level of serum albumin was also found to independently predict post-stroke pneumonia [53]. Neuroimaging parameters, such as infarct size, can also be associated with PSI, as demonstrated by one recent study [54]. Whether genetic polymorphism/s in inflammatory or immune-mediated genes are associated with susceptibility to and outcome of PSI is still under debate [55,56]. Possible candidate genes include *TNF- $\alpha$*  and *- $\beta$*  genes, *IL-6*, *IL-10*, *CD-14* and the Toll-like receptor (*TLR*)-4 genes [57].

### Stroke-induced immunodeficiency syndrome

Patients with acute stroke may also be at a higher risk of PSI because of a reduced ability to fight infections. Evidence from animal experiments supports the existence of a 'stroke-induced immunodeficiency syndrome' [58–60]. In one experiment, focal ischemic stroke induced an extensive apoptotic loss of lymphocytes and a shift from T helper (Th) cells to Th2 cytokine production, and these changes were associated with spontaneous bacteremia and pneumonia [60]. Prass *et al.* also found that stroke propagated bacterial aspiration to the development of pneumonia (even with very small bacterial colonies), and this propagation could be successfully prevented by  $\beta$ -adrenoreceptor blockade [61].

The CNS can modulate the activity of the immune system through complex neuro–humoral pathways, including the hypothalamus–pituitary–adrenal (HPA) axis, the vagus nerve and the sympathetic nervous system [62,63]. In one study, patients with acute stroke were found to have impaired cell-mediated immunity (e.g., reduced number of T lymphocytes) but not humoral immunity [64]. However, this study was uncontrolled and did not collect data on infection. Another study found that the immunosuppression after acute stroke may be endogenous. The authors demonstrated that plasma IL-1-receptor antagonist concentration is increased, and cytokine induction was suppressed, during the early recovery period after stroke [54]. On the other hand, immunosuppression after stroke might also

have potentially beneficial effects, such as by suppressing autoaggressive responses during lesion-induced exposure of CNS-specific antigens to the immune system [62]. Currently, there is insufficient knowledge about the frequency of stroke-induced immunodeficiency syndrome in man, the biological mechanisms that might underpin it and how long the syndrome lasts for [65].

### Post-stroke infection & recovery

Many studies have demonstrated that PSI may lead to poor functional outcome [24,29,48–51], but this finding is not universal across all studies, and the relationship between PSI and functional outcome remains unclear [20,66]. Owing to the complexity of the pathophysiological process of acute stroke, and the variation in the process of acute-stroke care, it is possible that previous studies of functional outcome have not completely adjusted for case-mix and other crucial factors that could have potentially affected the outcome. This could have led to false-positive (or -negative) correlations with functional outcome.

Although many studies have studied stroke-associated infections (SAIs), some have not distinguished between pre- and post-stroke infections, which might have potentially important differences in their prognosis. In particular, pre-stroke systemic infections usually result in a significant systemic inflammatory response (e.g., fever, tachycardia, hypotension and leucocytosis), which is already present at the onset of stroke (and remains for the first few hours or days of recovery). This can have potentially deleterious effects on the ischemic cascade, hence further impairing neuronal function and survival, leading to poorer functional outcome. In contrast, PSIs that occur several days or weeks after the initial event may not have the same effect on neuronal function and survival because the initial (and most damaging) pathophysiological processes may already have stabilized. We are currently testing these hypotheses through a large-scale prospective study.

### Effects of post-stroke infection on outcome

There is accumulating evidence that PSI may be associated with a poor short-term outcome, including in-hospital death, functional recovery and institutionalization on discharge; and these associations are independent of stroke severity, age and pre-stroke level of independence [24,48–51]. However, not all studies have found such an association [20,66]. PSI has been shown to

be one of the leading causes of death during the early recovery period after stroke [67–69]. One population-based study found that respiratory infections accounted for 22% of deaths during the first month, and for 26% of deaths during the first year after ischemic stroke [70]. From the German Stroke Register, pneumonia was the complication with the highest attributable proportion of death for the entire stroke population, accounting for 31% of all stroke-related deaths [16]. Kwan *et al.* found that patients who experienced PSI had three-times the probability of dying within the first 5 days compared with those who did not experience PSI [29]. In this study, the authors also showed that the association with short-term outcome was independent of case mix, stroke severity and adverse physiological disturbances including fever, hypoxia and hyperglycemia (which could also independently affect outcome) [29].

The correlation with early functional outcome has been less vigorously studied. In one prospective study, post-stroke pneumonia was significantly associated with poor functional outcome (Barthel index and Rankin score) and neurological status (NIHSS) [24]. In Kwan *et al.*, the authors also found an association between PSI and discharge destination, early post-stroke seizures and occurrence of pressure sores [29]. In this study, PSI was also found to increase the overall length of stay in the acute hospital by 7 days. Again, the interpretation of these findings can be complicated by the effects of the many potential confounding factors, such as stroke severity, case-mix and variations in process of acute stroke care. Hence, it may be difficult to draw definitive conclusion about the causality of these complex relationships.

The effects of PSI on longer-term outcomes are virtually unknown. In one study, post-stroke pneumonia was found to increase the relative risk of 1-month mortality threefold [51]. The relationship between PSI and longer-term outcomes, including motor and functional recovery, cognition, mood and quality of life, are currently being investigated in ongoing clinical studies.

#### Pathophysiological mechanism to explain influence on outcome

Post-stroke infection is responsible for the majority of the deaths occurring between 1 week and 1 month after stroke, peaking towards the end of the second week. During this highly unstable period of early stroke recovery, PSI may lead to neurological deterioration by causing

homeostatic disturbances (e.g., hyperglycaemia, fever, acidosis and excitotoxicity) [71–73], haemostatic activation (e.g., excessive thrombin generation and fibrin turnover) [74,75] and an overwhelming inflammatory response that can lead to hypotension and shock [76]. In one study, early neurological deterioration after the initial stroke was associated with an acute-phase response on admission, including higher leukocyte count, higher body temperature and a higher fibrinogen level [75].

PSI often leads to fever, and there is good evidence that fever is an independent predictor for higher mortality and morbidity after stroke [77]. The harmful effects of fever have been attributed to increased metabolic demands, changes in permeability of the blood–brain barrier, acidosis and an increased release of neurotransmitters [73,78]. Studies using animal models of focal and global ischemia have demonstrated that cerebral hyperthermia (over 39° C) can lead to larger infarct volume and more severe histological outcome [73,79–81]. However, in humans, the effects of PSI on other important physiological parameters, such as infarct volume, cardiovascular function, homeostatic control and cerebral hemodynamics remain unclear, but may individually affect outcome via different pathways.

#### Inflammatory response, infection & outcome

Markers of systemic inflammatory response are commonly raised after acute stroke, especially when PSI has occurred [82]. There is now good consensus that markers of acute-phase response such as highly sensitive (hs) C-reactive protein (CRP) could independently predict unfavorable outcome and stroke recurrence [83–85]. Furthermore, admission CRP also predicts mortality among patients treated with thrombolysis, and early recanalization does not ameliorate the negative prognostic impact of elevated CRP [86].

However, there is much controversy about whether inflammation is beneficial or harmful after ischemic stroke [87,88]. On the one hand, certain proinflammatory cytokines (e.g., IL-6 and TNF- $\alpha$ ) can enhance cell death, neurodegeneration and increase the extent of ischemic injury [87]. Moreover, inflammation can influence coagulation (i.e., prothrombotic) and endothelial dysfunction [89], which may lead to further microvascular compromise, as well as increasing metabolic demand by causing hyperthermia [87]. CRP may also induce inflammatory damage after stroke by activating matrix metalloproteinase [90]

as well as monocyte adhesion [91]. The integrity of the blood–brain barrier can also be disrupted after acute stroke, and the systemic immune system may encounter novel CNS antigens that can lead to CNS antigen-specific autoimmune response. It has been proposed that systemic infection after stroke may promote a deleterious CNS autoimmune response that could result in further neuronal damage and worse outcome [92]. However, recent evidence suggests that acute systemic inflammation may switch the phenotype of brain macrophages and microglia responding to neurodegeneration and promote an aggressive proinflammatory phenotype [93,94].

On the other hand, certain anti-inflammatory cytokines (e.g., IL-10) and even some proinflammatory cytokines (e.g., TNF- $\alpha$ ) have been shown to possess neuroprotective properties. Macrophages may also have neuroprotective and growth-promoting potentials in animal studies [88]. Clinical studies of anti-inflammatory agents (e.g., anti-ICAM-1 antibody and IL-1-receptor antagonist) have not demonstrated any significant benefit, but some clinical trials are still ongoing [95,96].

There are only a limited number of studies on the cytokine response in humans with PSI [54,82]. One small study found that patients with PSI had higher levels of certain types of proinflammatory cytokines, especially IL-6 and 55 kD soluble TNF receptors (sTNFR-p55), but not others such as IL-1 $\beta$ , TNF- $\alpha$  or sTNFR-p75 [97]. The authors suggested that local brain synthesis and systemic release of proinflammatory cytokines might precede the conventional systemic response to infection, such as fever, hepatic synthesis of acute phase proteins and leucocytosis.

### Diagnosing post-stroke infections

Early detection and treatment of PSIs has been highlighted as one of the possible reasons why organized stroke unit care leads to better survival and outcome [98,99], and certainly it has been incorporated as one of the major elements of acute-stroke management [100]. The most important aspect of managing PSIs is a low threshold for suspecting a diagnosis. However, in clinical practice it can be extremely difficult to be certain of the diagnosis, mainly because the clinical symptoms and signs can be difficult to establish, and what may be regarded as abnormal clinical findings of an infection may actually be common sequelae after stroke (unrelated to an infection). For instance, symptoms of pneumonia usually include productive cough and fever. However, after stroke, the cough reflex might be suppressed,

upper airway transmitted noises can frequently be heard because of poor swallow and fever can often be observed in the absence of infection. In the Copenhagen Stroke Study, 25% of acute stroke patients experienced fever, and of these only 16% had proven concurrent infection and 50% had a leucocytosis [101]. Moreover, clinical signs of pneumonia, such as inspiratory crackles and reduced breath sounds, are very nonspecific and can often be found in patients without pneumonia. In patients with communication and cognitive disability acquired through acute stroke, in particular, it may be difficult to establish a clear history (e.g., whether aspiration has occurred) and to carry out a full clinical examination (e.g., not understanding examiner's command), and hence to determine whether a PSI is present. For these reasons, diagnoses of PSI may be falsely made and treatment administered unnecessarily, or rehabilitative therapy unnecessarily interrupted, which can potentially lead to a longer hospital stay.

It is also unclear whether the accuracy of diagnosis of PSI is substantially increased with the aid of standard investigations. For example, the chest radiograph may show abnormal shadowing for reasons other than an infection, such as pulmonary edema and fibrosis. A negative chest radiograph does not exclude a diagnosis of pneumonia or lower respiratory tract infection. Urinary microscopy and culture may also be inaccurate when the patient has been catheterized, which is common practice in many acute stroke units [43]. Overall, the sensitivity and specificity of diagnosing PSI in the acute recovery period are currently unknown. New markers of bacterial sepsis (e.g., procalcitonin), some of which are available as bedside tests, may be more accurate in establishing a firm diagnosis of PSI [102–104]. In patients with head injury, a new qualitative IL-6 bedside test has been developed, and this test is claimed to be useful in predicting the risk of developing pneumonia [105].

### Management of post-stroke infections

The mainstay of treatment of PSIs is antibiotic therapy, either enterally (orally or via a nasogastric tube) or intravenously. Evidence from animal studies suggests that early or prophylactic antibiotic therapy could prevent the occurrence of PSIs and fever, and significantly reduce the risk of death or poor neurological outcome [106]. Sadly, this benefit has not been translated to human subjects. One clinical trial failed to demonstrate any benefit in administering prophylactic antibiotic therapy after acute stroke [18].



Interestingly, some pharmaceutical agents have been noted in clinical trials to reduce the risk of post-stroke pneumonia, including cilostazol (a phosphodiesterase inhibitor) [107], perindopril (an angiotensin-converting enzyme inhibitor) [108–112] and amantadine (an antiviral agent that also increases dopamine release from dopaminergic nerve terminals) [113]. Large-scale randomized trials involving these agents are not yet available. Certain antibiotic agents have also been found to possess neuroprotective properties in animal models of stroke. For instance, minocycline may be neuroprotective through its beneficial effects on inflammation, microglial activation, matrix metalloproteinases, nitric oxide production, oxidative stress and apoptotic cell death [114–116].  $\beta$ -lactam antibiotics might also be neuroprotective through preventing glutamate-induced neurotoxicity [117], although the mechanisms of action of  $\beta$ -lactam in this regard remain unclear. Owing to the good safety data and extensive experience with these agents, these antibiotics may have a potential to become neuroprotective treatments for acute stroke [118].

Many aspects of patient care that may potentially be important in preventing PSIs have not undergone formal evaluation through randomized controlled trials. For example, alternative methods of feeding (e.g., via nasogastric tube) have traditionally been regarded as safe and effective in avoiding aspiration of gastric content. However, this concept has been seriously challenged when one prospective study found that pneumonia occurred in 44% of tube-fed stroke patients [41], and in another study, 64% of bedridden tube-fed stroke patients suffered pneumonia [119]. Tube feeding was even found to be the strongest predisposing factor for PSI in another study [20]. The influence of positioning of the acute-stroke patient is also unclear. Although positioning has been found to influence arterial oxygen saturation and heart rate after stroke [120], the relationship between positioning and occurrence (or prevention) of PSI has not been investigated. Similarly, it remains unproven whether post-stroke pneumonia can be prevented by deep breathing exercises, speech and language therapy (from specialists who also provide swallowing assessment), or by the use of fluid thickener (to prevent aspiration). Avoidance of urinary catheterization in the acute recovery period is one obvious method of preventing UTIs [31], but many other strategies are also potentially beneficial. For example, the use of antimicrobial-impregnated urinary catheters, or the administration of an anti-

biotic agent at the time of catheterization, may prevent subsequent infection [121,122]. However, these hypotheses have not been formally tested in patients with acute stroke.

## Conclusion

After an acute stroke, PSI can complicate the recovery process and lead to a worse clinical outcome, including a higher risk of mortality. The effects of PSI on longer-term outcome and other aspects of recovery, such as cognition, mood and quality of life, are largely unknown. The cerebrovascular event itself may result in a systemic immunosuppressed state, hence lowering the threshold for subsequent systemic bacterial infections. Although there have been advances in the basic understanding of the pathophysiological mechanisms of PSI, clinical studies have not provided any clear guideline on the best methods of managing or preventing PSI.

## Future perspective

At the present time, the optimal management strategy for SAI in stroke patients is unclear. Future studies should adopt a combined translational approach to study the clinical phenomenology as well as the underlying mechanisms. In particular, future preclinical and clinical studies will better define the frequency and effects of stroke-induced immunosuppression, and how this relates to the neural and peripheral inflammatory response after stroke, and how this can in turn lead to the occurrence and long-term consequences of SAI. With better data from large and well designed longitudinal studies, it will be possible to seek out those patients who have just started developing an SAI (but before clinical manifestation), in whom immediate antibiotic therapy may help to avert a more severe SAI. Moreover, it will be possible to predict who will develop SAI in the subsequent few days, and who will have a poor outcome as a result of the SAI. For these patients, it may be possible to manage them differently to prevent the occurrence of or a bad outcome after an SAI.

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## Executive summary

- After an acute stroke, systemic infection can complicate the recovery process and lead to a worse clinical outcome, including a higher risk of mortality.
- The effects of post-stroke infection (PSI) on longer-term outcome and other aspects of recovery, such as cognition, mood and quality of life, are largely unknown.
- The cerebrovascular event itself may result in a systemic immunosuppressed state, hence lowering the threshold for subsequent systemic bacterial infections.
- Although there have been advances in the basic understanding of the pathophysiological mechanisms of PSI, clinical studies have not provided any clear guideline on the best methods of managing or preventing PSI.

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