Chapter 5
Infections After Stroke

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Abstract Infections are the most common medical complications after stroke, occurring in up to 65 % of stroke patients, and are associated with significant morbidity and mortality. Severe neurological impairment resulting from stroke, advancing age, and co-morbidities all increase the risk of infection after stroke. Stroke-induced immunodepression is also thought to play a role. Prevention as well as prompt recognition and treatment of infections are essential for reducing morbidity and mortality from stroke and may improve functional outcomes. There are recently completed and ongoing clinical trials to evaluate strategies for prevention and management of post-stroke infections.

Keywords Stroke • Post-stroke • Infection • Complications • Neurological deterioration

Key Messages

- Infections are the most common medical complications that occur during the acute phase of a stroke and are associated with poor short-term and long-term outcomes.
- There are several risk factors associated with the development of infection following stroke, including stroke severity, decreased conscious level, dysphagia, advancing age, medical co-morbidities, and stroke-induced immunodepression.
- Comprehensive structured assessment of all stroke patients should occur to identify post-stroke infection as a potential cause for early neurological deterioration.
- There are various clinical trials that are recently completed or currently recruiting subjects to examine the merits of prophylactic antibiotics for post-stroke infections.

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Introduction

Stroke is associated with a wide range of medical complications. Infections are the most common complications during the acute phase of stroke. Infections are the leading cause of death after the first day of stroke onset. Early neurological deterioration after stroke may be a sign of infection. Pneumonia and urinary tract infections are the most frequently observed infections. These are associated with poor outcomes that include neurological deterioration and disability, increased length of hospital stay, and death. This chapter focuses on the prevalence of post-stroke infections, risk factors, and measures for prevention and treatment of infections after stroke.

Prevalence of Post-stroke Infection

The rates of infection after stroke range between 5 and 65 % [1]. This wide variation is due to the varying population groups in the studies, definition of infection, and study design. Westendorp et al. conducted a systematic review of post-stroke infection and reported the pooled infection rate following stroke to be about 30 % (95 % confidence interval: 24–36 %); of the 30 %, pneumonia and urinary tract infection accounted for 10 % each [1]. That review pooled 87 studies, including cohort studies, stroke registries, and randomised control trials, involving 137,817 patients in total.

Urinary tract infection (UTI) is a common complication after stroke. The rates vary between 3 and 44 % [2]. One prospective cohort study of 412 stroke patients showed that 65 patients (15.8 %) had a UTI at a median of 14 days post-stroke [2]. Another study of 1,455 acute stroke patients recruited to a randomized controlled trial found an incidence of 17.2 % of UTI [3]. A third study of 489 unselected acute stroke admissions showed a UTI incidence of 16 % in the first week and 27.9 % at 3 months [4]. Davenport's study found an in-hospital UTI incidence of 16 % in 613 stroke patients [5]. Another multicentre study of 311 acute stroke patients reported the incidence of UTI to be 24 % [6].

Pneumonia is the most common infection after stroke. The incidence rates vary according to the cohort of stroke patients examined in various studies [7]. For example, the incidence in neurological intensive care units varies between 9.5 and 56.6 %; in medical intensive care units it ranges between 17 and 50 %, whereas in studies on patients in standard stroke units, the incidence was between 3.9 and 12 % [7]. The heterogeneous nature of the patients examined in these studies makes it difficult to make any meaningful comparisons between them [7].

Factors Associated with Post-stroke Infection

There are several risk factors associated with the development of infection following stroke. These include characteristics of study population (for example, patients

in intensive care units), stroke severity, decreased conscious level, presence of dysphagia, advancing age, female gender, and diabetes mellitus. The list below outlines the factors associated with the development of chest infections (pneumonia) after stroke.

Risk Factors Associated with Pneumonia After Stroke

- Aspiration—failure to clear secretions
- Dysphagia
- Nasogastric feeding
- Poor nutrition
- Immobility
- Reduced conscious level
- Cognitive impairment
- Reduced chest movement on affected side
- Reduced/dependence for oral care
- Current smoking
- Underlying conditions, e.g. diabetes, COPD, atrial fibrillation

There are various broad categories of pneumonia that occur following stroke: community acquired pneumonia, aspiration pneumonia, or health-care associated pneumonia [7]. Data suggests post-stroke pneumonia is often due to aspiration [7]. Unwell hospitalized patients routinely aspirate and patients with an impaired swallowing mechanism due to neurological injury are at especially high risk [8]. Pneumonia after stroke is associated with higher stroke severity (National Institute of Health Stroke Scale [NIHSS]) and depressed consciousness [7]. Consequently, infection rates were higher in intensive care unit (ICU) studies and in studies with a longer period of observation [7]. A review article by Hannawi et al. [7] identified various risk factors leading to pneumonia after stroke, including stroke severity measured by the NIHSS or the modified Rankin Scale [9–11], dysphagia [9, 12, 13], old age [4, 14], mechanical ventilation [10, 12, 13], APACHE II score/organ failure status [9], male sex [12], brain stem infarction [13], multihemispheric infarction [13], nonlacunar basal ganglia infarct [10], atrial fibrillation [11], admission from a nursing home [15], dysarthria [12, 16], altered level of consciousness, coma, or abnormal papillary exam [10], diabetes, congestive heart failure, chronic obstructive pulmonary disease or smoking, history of pneumonia, and low serum albumin level [9].

Recently, Hoffmann et al. developed a clinical A2DS2 score to predict pneumonia in acute ischaemic stroke and validated using data of two independent stroke registers [17]. This 10-point risk score (points) includes age ≥75 years (1), atrial fibrillation (1), dysphagia (2), male sex (1), stroke severity according to the National Institute of Health Stroke Scale 0–4 (0), 5–15 (3), and ≥16 (5) [17]. The proportion of pneumonia varied between 0.3 % in patients with a score of 0 points and 39.4 % in patients with a score of 10 points.

Risk Factors Associated with Urinary Tract Infection

Urinary tract infections (UTI) after stroke are associated with urethral catheterization, stroke severity ($p = 0.01$), decreased conscious level, greater post-stroke disability (higher modified Rankin score), advancing age, acute urinary retention, and increased post-void residual urine volume (PVR) [1, 2, 18]. A study reported that UTI is more common if PVR is over 100 ml irrespective of gender and age. Close monitoring of PVR and appropriate intervention is therefore needed to reduce the occurrence of UTI in stroke patients [18]. The common risk factors, such as female sex, diabetes mellitus, obstructive uropathy (enlarged prostate, renal stones), and oestrogen deficiency, can also predispose to UTI in stroke patients.

Immunosuppression After Stroke

Another emerging concept of increased susceptibility to infections following stroke is one of post-stroke immunodepression [19]. Counter-regulatory responses, triggered by the pro-inflammatory response to stroke, appear to effect systemic immunodepression via suppression of both innate and adaptive immune responses. A range of anti-inflammatory and immunosuppressive changes have been identified in experimental and clinical studies, including reduced mononuclear phagocyte and natural killer cell function, induction of anti-inflammatory cytokines, apoptotic lymphocyte loss, and altered T lymphocyte activity. Stroke-induced immunosuppression mainly results from the activation of sympathetic mediated pro-inflammatory cytokine production. In contrast, the vagus nerve releases acetylcholine which inhibits the production of pro-inflammatory cytokines, but maintains the production of anti-inflammatory cytokines [8, 20–22]. Those mechanisms are part of the "central nervous system injury-induced immune deficiency syndrome" mediated by the sympathetic nervous system, the N. vagus (parasympathetic nervous system), and the hypothalamo–pituitary–adrenal (HPA) axis [23]. The identification of markers of immunodepression in the early post-stroke phase may prove useful for identifying patients who may have increased susceptibility to infection. It also seems likely that post-stroke immunodepression will need to be taken into account where stroke treatments impact upon inflammatory and immune pathways [19].

Organisms Causing Infection After Stroke

In clinical practice, it is fairly common for no causative organism to be detected in post-stroke pneumonia. This is due to difficulty in collecting sputum or aspirate for culture due to neurologic deficit or lowered level of consciousness, some cases of suspected pneumonia actually being non-infectious aspiration pneumonitis, or infection could be caused by anaerobic bacteria that require special culturing

techniques [1]. A systematic review that examined the data of patients with post-stroke pneumonia to identify microorganisms reported that the organisms were mainly those associated with early onset nosocomial pneumonia, or a community acquired aspiration syndrome [1]. These included Streptococcus species, Staphylococcus aureus and gram-negative bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli or Enterobacter species. Gram-negative bacteria and Staphylococcus aureus are known to cause pneumonia by aspiration of endogenous material from the colonized oropharynx and are often seen in nosocomial infections [24]. Streptococcus species is still the most detected pathogen in community acquired pneumonia [25]. In stroke patients, it could be a cause of 'community acquired aspiration pneumonia', with aspiration occurring at the time of stroke [26].

Stroke Outcome and Post-stroke Infection

Infections following stroke are associated with worse short-term and long-term outcomes. In pooled analyses by Westendorp et al., the mortality rate in patients with infection was 48 % versus 18 % in patients without infection [1]. Kwan et al. conducted a study of 439 patients (398 with stroke and 41 with transient ischaemic attack) exploring the clinical consequences of post-stroke infections [27]. They found that patients with post-stroke infections were more likely to develop other complications such as pressure sores and seizures. Furthermore, post-stroke infections were significantly associated with in-hospital mortality and institutionalization on discharge [27]. In a consecutive cohort study that looked at 521 acute stroke patients, stroke-associated infection was independently associated with poor functional outcome at discharge and at 1 year [28]. Pneumonia is the most common post-stroke infection and has been associated with a relative risk of 3.0 for mortality in a study of 14,293 patients with stroke [15]. In pooled analyses of effects of infection on outcome after stroke, pneumonia was significantly associated with in-hospital mortality [1]. Mortality rates were also higher in patients with pneumonia (26 % vs. 5 %) than those without pneumonia [1]. Post-stroke pneumonia also increases the financial burden on the medical system, with the annual cost of this complication reported to be about $459 million US [14].

Stott et al. found that in a study of 412 stroke patients, UTI was associated on univariate analysis with an increased risk of death and/or post-stroke disability at 3 months after stroke [2]. They postulated biologically plausible reasons for UTI causing a worse outcome after stroke: (1) During the acute phase of a UTI, UTI-induced systemic inflammation and raised temperature may cause further damage to vulnerable brain tissue in the ischaemic penumbra [29–31]. (2) Infections are associated with a catabolic response, with loss of skeletal muscle; this is likely to be due to multiple complex factors, including inflammation and cytokine release, increased glucocorticoids and activation of the sympatho-adrenal axis [32]. The associated loss of skeletal muscle is likely to adversely affect physical rehabilitation.

Clinical Assessment and Investigations

Infections are a recognised cause of morbidity and mortality following stroke. Neurological deterioration and changes in physiological parameters associated with stroke can make it more difficult to diagnose infections. It is quite common for fever and inflammation to develop after stroke as a result of disturbance of the thermoregulatory centre and an acute phase response, respectively [33, 34]. Since infections are common after stroke, a search for infection should still be undertaken and antibiotics given when appropriate [34]. Non-specific clinical indicators of infection also include delirium, neurological deterioration, and dehydration. Furthermore, infection can impede rehabilitation. Since pneumonia and UTI are the most common infections, initial investigations should include a chest radiograph, urinalysis with a mid-stream urine sample sent for culture, and blood cultures if pyrexial. However, raised inflammatory markers could also be associated with other complications, such as deep-vein thrombosis, pressure sores, and seizures, or may be indicative of the cause of stroke, such as vasculitis or infection (infective endocarditis). If any of these are suspected, clinical correlation is necessary followed by the appropriate investigations.

Potential Strategies to Minimise Post-stroke Infection

Urinary Tract Infection

There are various recommendations that can reduce the prevalence of urinary tract infection (UTI) following stroke. Usual methods for preventing UTI are adequate hydration, use of cranberry juice, and oestrogen supplementation (topical) [35]. In hospitalized patients, other strategies include improving mobility with physiotherapy, preventing constipation, and avoiding or minimising the use of urinary catheters [35]. Minimising and avoiding unnecessary catheterization is probably the single most effective strategy in preventing UTI [36]. In certain circumstances it is necessary to use a urinary catheter, such as in acute urinary retention due to urethral obstruction (enlarged prostate, stone) or neurogenic bladder (stroke, multiple sclerosis, spinal injury), urological surgery, to allow healing of sacral pressure sores, and accurate measurement of urine output in critically ill patients [37]. It may be possible to reduce the risk of associated infection by early removal, vigilance in catheter-care, or by use of modified catheters coated with antimicrobials. A structured reminder to nurses by physicians to remove unnecessary catheters in ICU has been shown to reduce duration of catheterization and associated infections [38]. High aseptic standards of catheter care, correct positioning of the drainage tubing and collection bag, and maintaining a closed system may all help to reduce the risks of clinically significant infection [39]. Using modified catheters such as nitrofurazone-coated silicone or silver-coated latex may reduce the risk of infection with short-term catheterization [39, 40].

Chest Infection (Pneumonia)

Bearing in mind that aspiration is an important risk factor for chest infection after stroke, appropriate management of dysphagia following stroke is vital in reducing chest infections. A strict vigilant swallowing assessment after stroke is important. The most widely accepted measure is to keep a stroke patient nil by mouth until the swallow has been formally assessed [41]. Formal swallow assessment including a water swallow assessment also significantly reduces the risk of pneumonia [42, 43]. It has been shown that patients having intensive (daily) standard swallow therapy developed fewer chest infections secondary to aspiration compared to those receiving usual care (26 % vs 47 %) [44]. Nasogastric feeding or percutaneous gastrostomy tube are common ways of providing nutrition to stroke patients who have an unsafe swallow. However, these methods do not eliminate the occurrence of pneumonia, since aspiration of oral contents may continue [45]. A recent Cochrane review of the clinical trials showed no difference between these two methods regarding the occurrence of pneumonia in patients with dysphagia; however, percutaneous gastrostomy tube was safer and more effective in terms of feeding [46]. Regular oral hygiene is also important in reducing the development of chest infections.

Early mobilisation and good pulmonary care have also been shown to reduce the risk of pneumonia [47–49]. Preventative measures include body positioning to maintain airway patency (usually in a semi-recumbent position), suctioning of accumulated secretions, and early mobilisation [47]. In a population-based Danish follow-up study, mobilization within the first day post-admission was associated with a substantially lower risk of pneumonia and UTI [49]. Cuesy et al. conducted a randomised controlled trial of 223 acute stroke patients that implemented a "turn-mob program": turning and passive mobilization carried out by a previously trained relative [50]. This is a mobilization programme in bed that involves changing a patient's position (e.g. from lateral recumbent to supine) and mobilising all four limbs for 10 s ten times. The trial showed that there was a relative risk reduction of 0.39 in the incidence of nosocomial pneumonia. The "turn-mob" program applied on patients during the acute phase of an ischaemic stroke decreases the incidence of pneumonia [50].

There are various clinical trials that have recently been completed or are currently recruiting stroke subjects to examine the management and prophylaxis of post-stroke infections [51–55]. The Early Systemic Prophylaxis of Infection After Stroke (ESPIAS) was a randomized, double-blind, placebo-controlled study of antibiotic prophylaxis in 136 acute stroke patients using intravenous levofloxacin or placebo in addition to optimal care [52]. That study showed that prophylactic levofloxacin was no better than optimal care for the prevention of infections in stroke patients [52].

The Mannheim Infection in Stroke Study (MISS) was another randomised, controlled study of antibiotic prophylaxis in 60 acute stroke patients using prophylactic mezlocillin plus sulbactam for 4 days versus conventional management [53]. That study showed that the intervention lowered the rate of all cause infection ($p<0.01$) and may be associated with a better clinical outcome ($p=0.01$), though it was not powered enough for clinical outcomes.

The Preventive ANtibacterial THERapy in acute Ischaemic Stroke (PANTHERIS) was a randomised, double-blind, placebo controlled trial in 80 acute stroke patients using intravenous moxifloxacin [54]. The study showed that at 11 days, on intention to treat analysis, the infection rate was non-significantly lower in the treated group compared to placebo (15.4 % vs 32.5 %). In this study, neurological outcome and survival were not significantly influenced by treatment with moxifloxacin [54].

The Stroke Infection study (STROKE INF) is a cluster randomised trial of different strategies of antibiotic use to reduce the incidence and consequences of chest infection in acute stroke patients with dysphagia [55]. The study aims to recruit 1,200 acute stroke patients and randomise them to receiving prophylactic amoxicillin (or equivalent co-amoxiclav) and clarithromycin for 7 days. Outcome measures include incidence of chest infection, functional outcomes, and mortality.

The treatment of stroke-associated pneumonia is prompt early use of antibiotics using the local hospital guidelines for aspiration and/or hospital acquired infections, as these are the most common chest infections after stroke. The decision of empirical antibiotic treatment depends on the individual's risk factors, disease severity, time of onset, and general microbiology of pneumonia [7, 56].

Infections Associated with Stroke

In this chapter, we have discussed infections after stroke. It is also important to note that various infections have also been associated as potential risk factors *for* stroke [57]. Acute systemic infections that cause vasculitis (inflammation of the blood vessels) or infective embolisation; examples include infective endocarditis, meningitis (bacterial, fungal, and tuberculous), human immunodeficiency virus (HIV), herpes zoster, neuro-syphilis, hepatitis B or C, Rickettsial diseases, Helminthic infections, and Chagas disease [57]. The association between these acute infections and stroke is due to the pro-coagulant state caused by the inflammatory response induced by these infections rather than the actual microbial agents. Chronic infections such as upper respiratory infections, urinary tract infections, Helicobacter pylori infections, and periodontal infections have also been associated with stroke, although their exact patho-physiological mechanisms or indeed their causal relationship is not yet fully established [57].

Conclusion

Although infections are the most common medical complications after stroke, the reported rates of infection vary considerably. Pneumonia is the most common type of post-stroke infection, probably followed by urinary tract infection. Stroke severity is an important determinant of susceptibility to infection. This can be due to the degree of neurological impairment directly caused by stroke or the consequences

of neurological impairment relating to feeding and nutrition, mobility, invasive medical devices, and suboptimal acute stroke care. Preventative measures revolve around the consequences of stroke, specifically early involvement of the stroke multi-disciplinary team for regular intensive therapy, use of stroke care pathways, and consideration of potential risk factors such as urinary catheters. Stroke patients are at high risk of developing infection, therefore careful clinical assessment is needed to make a diagnosis so that antibiotic therapy can be started promptly. There is ongoing research into methods of prevention and management of post-stroke infections.

Patient Questions

Q. What are common infections that occur following a stroke?

A. The two most common infections following stroke include chest infection and urinary tract infections.

Q. What are the reasons for these infections to occur following a stroke?

A. There are several risk factors that predispose stroke patients to develop infections. Risk factors for developing chest infections following a stroke include aspiration (failure to clear secretions), swallowing difficulties, artificial tube feeding, poor nutrition, prolonged immobility, reduced conscious level, cognitive impairment, reduced chest movement on affected side, reduced/dependence for oral care, and current smoking.

Risk factors for developing a urinary tract infection following a stroke include female sex, diabetes mellitus, obstructive lesions (enlarged prostate, renal stones), oestrogen deficiency (atrophic vaginitis), urethral catheterization, decreased conscious level, and advancing age.

Q. Can infections following stroke be prevented?

A. Simple measures to minimise urinary tract infections include adequate hydration, oestrogen supplementation, improving mobility, preventing constipation, and avoiding the use of urinary catheters. Simple measures to reduce the incidence of chest infections include regular swallowing assessment to minimise aspiration, regular oral hygiene, early mobilisation, and judicious use of artificial feeding methods.

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