

Infection in Patients with Acute Stroke

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Abstract: Stroke is a major cause of mortality and morbidity worldwide and efforts to reduce the impact of the disease are strongly needed. Patients with acute stroke have an increased risk of in-hospital complications, in particular pneumonia and urinary tract infections. These infections are associated with an adverse patient outcome and increased health care costs. Here we review the existing knowledge on the risk and consequences of post-stroke pneumonia and UTI in adult patients and discuss the evidence of possible targets for intervention.

Keywords: Stroke, infections, incidence, clinical outcome, pneumonia, urinary tract infection.

INTRODUCTION

Stroke has a major global impact on mortality and morbidity. It is responsible for nearly six million deaths every year and thereby claims more lives than AIDS, tuberculosis and malaria put together [1-4]. Furthermore, it is a leading cause of permanent disability worldwide [5].

Patients with stroke are susceptible to a wide array of medical complications which have been linked with the clinical outcome. Infections, in particular pneumonia and urinary tract infections (UTI), are among the most frequent complications. Effective prevention and treatment of infections should therefore be an important component in any strategy aiming to reduce the impact of stroke.

Here we review the existing knowledge on this risk and consequences of post-stroke pneumonia and UTI in adult patients and discuss the evidence of possible targets for intervention.

MECHANISMS LEADING TO POST-STROKE INFECTIONS

A number of different mechanisms may increase the risk of infections in by patients with stroke (Fig. 1). These mechanisms may both be direct consequences from the brain injury caused by the stroke and indirect mechanisms caused by factors associated with but not caused by the stroke (eg., high age and comorbidity).

Symptoms Caused by the Stroke

As a direct consequence of the stroke, the patients often experience symptoms that may facilitate infections. These symptoms include immobility, dysphagia which increases the risk of aspiration, impaired cough reflexes and bladder dysfunction. The adverse impact of these symptoms on the risk of infections may be further strengthened by the difficulties or even inability of the patients to communicate and cooperate due to coma, aphasia, dementia and/or delirium.

Stroke Related Treatments

Invasive procedures such as urinary catheters, intravenous lines and tubes used for mechanical ventilation constitute easily accessible routes for entering the body for pathogens. Permanent urinary catheters is associated with a particular high risk as it is associated with an absolute risk of urinary tract infections of 3-10% per day of catheterization leading to an almost 100% risk after 30 days in general medical populations [6,7].

Brain-Induced Immunodepression

A growing body of evidence indicates that central nervous system mediated impairment of immune competence may lead to systemic infections in patients with central nervous system injuries including stroke, brain tumors, epilepsy, and traumatic brain injury [8-10]. The immunodepressive effect of central nervous system injuries is mediated through a number of humoral and neural pathways which include the hypothalamic pituitary adrenal axis, the vagus nerve and the sympathetic nervous system [8]. Reported defects in immune function in patients with stroke include reduced peripheral blood lymphocyte counts, impaired T- and natural killer cell activity, and reduced mitogen induced cytokine production and proliferation [8,9].

Patient Characteristics Related with Stroke

Patients with stroke often have comorbidities including diabetes, chronic obstructive pulmonary disease and cancer which may increase the susceptibility for infections and complicate the prevention and treatment.

LITERATURE SEARCH

We conducted a systematic literature search in international databases in order to identify scientific publications that reports on in-hospital pneumonia and UTI in patients with stroke during hospitalization with a focus on risk, risk factors, and consequences.

The systematic search was initially conducted in *PubMed*, and followed by searches in *The Cochrane Database* and *Google Scholar*. The search strategy was based on a combination of free-text and MESH-terms search:

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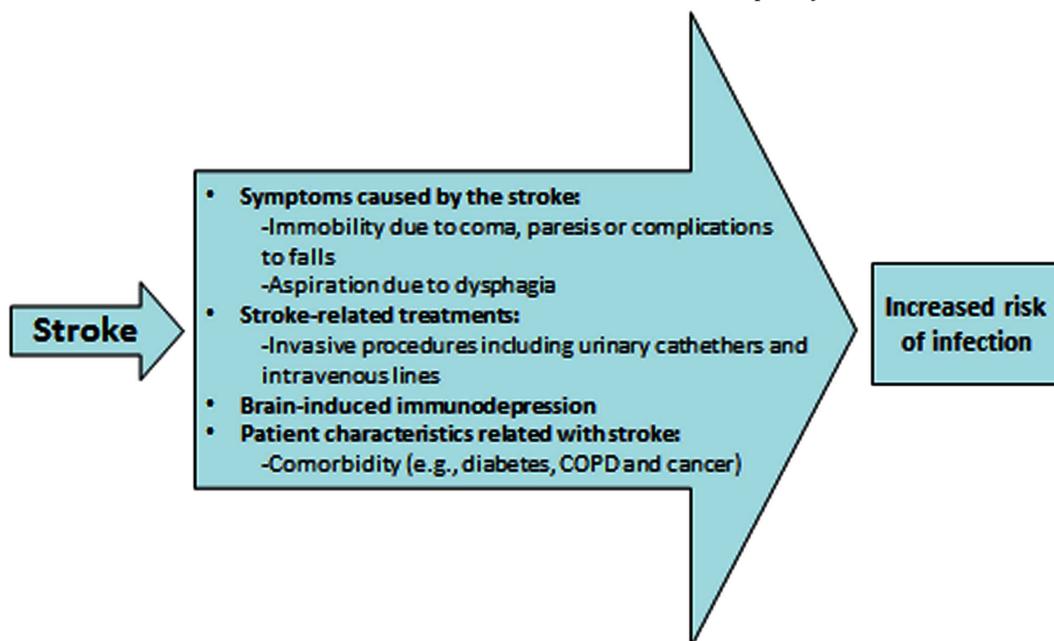


Fig. (1). Mechanisms leading to increased risk of post-stroke infections.

“Cerebrovascular Accident”, “Cerebrovascular Disorders (MESH)”, and “Stroke (MESH)”, in combination with “pneumonia” and “urinary tract infection”. The search was limited to include articles published in English and involving people age 18 or over. The literature and information search was completed in October 2011.

RISK OF POST-STROKE PNEUMONIA AND UTI

Pneumonia

Post-stroke pneumonia has been reported to occur during hospitalization 1.2% to 22% of patients admitted with acute stroke in the studies identified in our literature search [11-41]. In a recent meta-analysis of 87 studies, Westendorp *et al.* reported a pooled estimate of 10% (95% confidence interval [CI] 9-10%), but also found significant heterogeneity between the studies with studies on intensive care unit patients reporting a substantially higher risk (28%, 95%CI 18-38%) [42].

Most medical complications and in particular pneumonia occur early, often as early as within the first 24 hours and rarely after 4 days [13]. Pneumonia is the most common cause of fever within the first 48 hours after an acute stroke [24,43]. Most stroke-related pneumonias are believed to result from aspiration [24].

A range of independent patient-related predictors of post-stroke pneumonia have been identified. The findings are not entirely consistent but the list of predictors appear to include older age (>65 years), preadmission dependency, speech impairment, severity of post-stroke disability, cognitive impairment, dysphagia, type of stroke (nonlacunar ischemic stroke) and comorbidities (chronic obstructive pulmonary disease, coronary artery disease) [32,39].

UTI

The reported risk of in-hospital UTI varies substantially in the available studies with risks ranging from 3.7% to

65.8% (Table 1). In their meta-analysis, Westendorp *et al.* found a pooled estimate of 10% (95%CI 9-12%) [42]. As for pneumonia, the risk of UTI appears to be substantially higher in ICU patients (pooled estimate 20%, 95%CI 0-40%) [42]. The median time from admission to post-stroke UTI has been reported to be 15-17 days [25, 28]. Factors found to predict UTI include stroke severity, depressed consciousness level, increased post-void residual urine volume, and diabetes mellitus [13,27,28]. The majority of hospital-acquired UTIs are associated with the use of indwelling catheters [28,44] but whether catheterized or not, patients with stroke have more than double the odds for a UTI when compared with the general medical and surgical populations [30].

CONSEQUENCES OF PNEUMONIA AND UTI IN PATIENTS WITH STROKE

Infections have been associated with a poor outcome in patients with stroke because they may hinder optimum rehabilitation, increase the length of hospital stay and resource use and increase case-fatality [8]. In a recent population-based Danish study, pneumonia (adjusted ratio of length of stay 1.80, 95%CI:1.54–2.11) and UTI (adjusted ratio of length of stay 2.29, 95%CI:1.88–2.80) were associated with substantially longer length of hospital stay even after adjusting for a wide range of possible confounding factors [50]. The increased length of stay is of major importance since length of stay has been identified as the main cost-determining factor for patients with acute stroke.

Overall, post-stroke infections have in a recent meta-analysis also been shown to be associated with higher case-fatality rates (crude OR 2.08, 95% CI 1.63 - 2.67) [42]. The corresponding crude ORs of death associated with pneumonia and UTI were 5.58 (95% CI: 4.76-6.55) and 1.12 (95% CI: 0.76, 1.66), respectively, in the metaanalysis [42]. Table 1 presents studies with focus on the association between post-stroke pneumonia, UTI and case-fatality. There

Table 1. Selected Studies on the Association Between Pneumonia, UTI and Case-Fatality Among Patients with Stroke

Author, Year and Country	Sample Size, Design, and Setting	Type of Complication	Period of Mortality Reported	Case-Fatality (%)	Adjusted Relative Mortality Estimates
Stott 2009 [28] Scotland 2009	N= 412 Prospective IS + HS Acute/sub acute Single center	UTI	3 months	UTI:15.8	UTI associated with death or disability at 3 months, but not significantly.
Vermeij <i>et al.</i> 2009 [29] The Netherlands	N= 521 Prospective IS Acute /sub acute Multicenter	Pneumonia UTI	1 year	Any stroke-associated infection: 47.0	Any stroke-associated infection: Adjusted HR 1.5 (95% CI:1.0–2.4) Pneumonia: Adjusted HR 2.1 (95 %CI: 1.2–3.7)
Sapoznik <i>et al.</i> 2008 [45] Canada	N= 489 Prospective IS + HS Acute/sub acute Single center	Pneumonia	30 days case-fatality 1 year		30 days: OR 1.91 (95% CI: 1.23–2.95) 1 year: OR 2.21 (95% CI: 1.53–3.19)
Kwan <i>et al.</i> 2007 [31] UK	N = 439 Prospective IS+ TIA (9% acute Single center	Pneumonia, UTI	In-hospital mortality	With/without infection:26.0/9.6	Adjusted OR: 2.50 (95% CI: 1.27–4.90)
Ovbiagele <i>et al.</i> 2006 [33] US	N= 663 Prospective IS Multicenter	Pneumonia UTI	In-hospital mortality	With/without pneumonia: 27.3/5.3 With/without UTI:8.3/7.4	Pneumonia: Adjusted OR: 5.96 (95%CI:3.02–11.70) UTI: Adjusted OR: 0.83 (95% CI:0.43–1.57)
Kimura <i>et al.</i> 2005 [46] Japan	N = 15,322 Prospective IS + TIA (complete follow-up: 71.7%)	Pneumonia	1 year		Cause of dead: Pneumonia: 22.6%
Asaylan <i>et al.</i> 2004 [35] UK	N= 1,455 RCT IS Acute/sub-acute Multicenter	Pneumonia UTI	3 months		Pneumonia: Adjusted HR 2.2 (95% CI:1.5–3.3) UTI: Adjusted HR 1.0 (95% CI:0.7–1.6).
Katzan <i>et al.</i> 2003 [47] US	N =11,286 Prospective IS + HS Acute/sub-acute Multicenter	Pneumonia	30-days mortality	With/without pneumonia:26.9/4.4	Adjusted RR 2.99 (95% CI:2.44–3.66).
Hamidon <i>et al.</i> 2003 [36] Singapore	N= 163 Prospective IS Acute Single center	Pneumonia UTI	In-hospital		Pneumonia/UTI: OR 14.8(95% CI: 4.31–51.1).
Tirshweel <i>et al.</i> 1999 [48] US	N=4,757 Prospective IS Multicenter		In-hospital		Pneumonia: Adjusted OR 3.7 (95% CI:2.8–4.8). UTI: Adjusted OR 0.6 (95% CI:0.4–0.8)
Silver <i>et al.</i> 1984 [49] Canada	N= 1,073 Prospective IS +HS Acute Single center	Pneumonia	In-hospital 2.- 4.th. week after admission	IS: Pneumonia 28/79 = 35.4 HS: Pneumonia 2/10 =20.0	NR
Ingeman <i>et al.</i> 2011 [50] Denmark	N=13,721 Prospective IS + HS Acute/sub acute Multicenter	Pneumonia UTI	30 day 1 year	Pneumonia: 30 day: 24.9 1 year: 50.9 UTI: 30 day: 7.3 1 year: 31.8	Pneumonia: 30 day: Adjusted HR 1.59 (95% CI:1.31–1.93) 1 year: Adjusted HR 1.76 (95% CI:1.45–2.14) UTI: 30 day: Adjusted HR 0.45 (95% CI:0.38–0.54) 1 year: Adjusted HR 0.94 (95% CI:0.84–1.05)
Finlayson <i>et al.</i> 2011 [39] Canada	N=8,251 prospective Registry based IS acute/sub acute Multicenter	Pneumonia	30 day 1 year		30 day: OR 2.2 (95% CI:1.8-2.7) 1 year: OR 3.0 (95% CI: 2.5-3.7)

NR= not reported HS= Hemorrhagic stroke IS= Ischemic stroke RCT=randomized controlled trial.

are major variations between the studies in design, size, length of follow-up and possibility of confounder control, however, altogether, the majority of the existing studies have shown that post-stroke pneumonia is a strong predictor of both short- and long-term mortality, and suggested that proper management of pneumonia may improve short- and long-term prognosis for patients with acute stroke. A number of studies have found pneumonia to be a leading cause of death in the post-acute phase of stroke accounting for approximately one in three in-hospital deaths [34,47]. In contrast, data on UTI are more limited and inconsistent with some studies finding no significantly increased risk of mortality and others finding UTI to be associated with a decreased risk of in-hospital mortality.

The exact mechanisms underlying the association between post-stroke infection and poor clinical outcome are not well-defined. Several factors may be at play, including the factors also driving the increased risk of infections (Fig. 1). In addition, increasing evidence demonstrate that immunity and inflammation are key elements of the pathobiology of stroke and may also play a central role in relation to the clinical impact of post-stroke infections [51]. Thus, experimental data suggest that animals subjected to a systemic inflammatory insult simulating an infection at the time of stroke are predisposed to develop an autoimmune response to the brain, and that this response is associated with worse outcome [52].

POSSIBLE TARGETS FOR INTERVENTION

Given the high risk and the adverse effects of post-stroke infections, it is obviously of major importance to identify effective methods for reducing the risk of infections in patients with stroke. Promising targets for intervention includes:

Preventive Use of Antibiotics

A number of trials have in recent years evaluated preventive use of antibiotics in patients with acute stroke. Westendorp *et al.* identified 5 randomized clinical trials in their systematic review from 2012 [53]. The trials included a total of 506 patients of whom 94% had ischemic stroke. Study interventions were fluoroquinolones (2 studies), tetracycline (1 study), penicillin (1 study) or a combination of beta-lactam antibiotic with beta-lactamase inhibitor (1 study). Therapy was in all studies started within 24 hours of stroke onset and lasted between 3 and 5 days. Overall, the risk of infection was significantly lower among the patients receiving antibiotics group than among patients in the placebo/control group (22% versus 36%, corresponding to a pooled RR for infection of 0.58, 95% CI: 0.43-0.79). Thirty-three of 248 patients (13%) in the antibiotic group died compared with 38 of 258 (15%) in the placebo/control group (pooled RR for mortality 0.85, 95% CI: 0.47-1.51). No major harm or toxicity was reported. Although promising, the small scale and the conflicting results of the individual trials warrant further evaluation of preventive antibiotics in large scale clinical trials before any firm recommendations on routine use of preventive antibiotics can be made [53,54].

Reducing Use of Permanent Urinary Catheters

Because use of urinary catheters is so strongly associated with the risk of UTI both in the general medical population and in patients with stroke, reducing the use or decreasing

their infectious risk will lower the risk of UTI [55]. Antiseptic-coated catheters, including silver alloy and antibiotic-impregnated catheters, appear to reduce the risk of asymptomatic bacteruria, however, so far only small scale studies have been published and studies on symptomatic UTI are lacking [55]. Educational interventions and other methods to reduce inappropriate use of permanent catheters have also been examined and found promising although randomized data from stroke populations are lacking [55]. Alternatively, intermittent catheterization methods or, in men, condom catheters may be used to avoid permanent indwelling catheters.

Organized In-Patient Care

In a Cochrane review, which included three randomized clinical trials and 12 nonrandomized studies, patient management with stroke care pathways was found to be associated with a lower risk of developing certain complications, including UTI [56]. No statistical significant differences in risk were found for other complications such as pneumonia, deep venous thrombosis, and pressure sores; although the point estimates indicated that patient management with stroke care pathways might have a protective effect. Numerous trials have also documented the efficacy of stroke unit care [57]. Many questions remain about the specific processes responsible for this effect; however, a key difference between stroke unit care and general wards seems to be earlier initiation of rehabilitation and mobilization and careful monitoring of clinical parameters [57]. Early mobilization appears to play a pivotal role in reducing the risk of complications including infections. In a population-based Danish follow-up study, mobilization within the first post-admission day was associated with a substantially lower risk of pneumonia (adjusted OR 0.43, 95% CI:0.34–0.54) and UTI (adjusted OR 0.56, 95%CI:0.47–0.66) [38]. The advantage of early mobilization was also confirmed in a recent randomized clinical trial, where early mobilization in the form of passive turning and mobilization during the acute phase of an ischemic stroke decreased the incidence of pneumonia [58]. The optimal timing of mobilization has so far been unclear, but mobilization within the first few days seems to be well tolerated and not harmful [59].

Early assessments of swallowing is another tool considered essential for preventing aspiration although there is only limited data on the accuracy of the available screening methods and the effectiveness of subsequent interventions in high risk patients, including patients with reduced consciousness and swallowing disturbances.

Recommendations from the American Heart Association [60] and the European Stroke Initiative [61] on prevention of infections in patients with stroke are summarized in Table 2.

CONCLUSIONS

Infections, in particular pneumonia and UTI, are common complications in patients admitted with acute stroke and associated with an adverse outcome. The infections are often preventable or, when prevention is not possible, amenable to early recognition and treatment in order to avoid serious consequences. Use of care pathways in acute stroke care and an early multidisciplinary effort to ensure optimal care, in

Table 2. Recommendations from the American Heart Association [60] and the European Stroke Initiative [61] on Prevention of Infections in Patients with Stroke

Area	American Heart Association	European Stroke Initiative
Preventive use of antibiotics	Prophylactic administration of antibiotics is not recommended (Class III, Level of Evidence B).	Prophylactic administration of antibiotics is not recommended, and levofloxacin can be detrimental in acute stroke patients (Class II, Level B)
Reducing use of permanent urinary catheters	If possible, the placement of indwelling bladder catheters should be avoided because of the associated risk of urinary tract infections (Class III, Level of Evidence C). Some patients may need prolonged catheter drainage of the bladder, and measures to lower risk of infection should be taken.	In stroke patients with urinary incontinence, specialist assessment and management is recommended (Class III, Level C)
Early mobilization	Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended (Class I, Level of Evidence C).	Early mobilization is recommended to prevent complications such as aspiration pneumonia, DVT and pressure ulcers (Class IV, Good Clinical Practice)
Swallowing assessment	Assessment of swallowing before starting eating or drinking is recommended (Class I, Level of Evidence B).	Swallowing assessment is recommended but there are insufficient data to recommend a specific approach for treatment (Class III, Good Clinical Practice)
Nutrition	Patients who cannot take food and fluids orally should receive nasogastric, nasoduodenal, or PEG feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing (Class IIa, Level of Evidence B). The timing of the placement of a PEG is uncertain. Nutritional supplements are not needed (Class III, Level of Evidence B).	Oral dietary supplements are only recommended for non-dysphagic stroke patients who are malnourished (Class II, Level B) Early commencement of nasogastric (NG) feeding (within 48 hours) is recommended in stroke patients with impaired swallowing (Class II, Level B) It is recommended that percutaneous enteral gastrostomy (PEG) feeding should not be considered in stroke patients in the first 2 weeks (Class II, Level B)

particular early mobilization and minimized use of permanent urinary catheters, appear to be effective in reducing the risk of infections.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

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Received: January 2, 2012

Revised: June 20, 2012

Accepted: July 15, 2012

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