Post-stroke Infections – Diagnosis, Prediction, Prevention and Treatment to Improve Patient Outcomes

Hendrik Harms,[1] Elke Halle[2] and Andreas Meisel[3]

1. Clinical Scientist, Centre for Stroke Research Berlin, and Attending Neurologist, Department of Neurology, Charité Medical University Berlin; 2. Clinical Scientist, and Attending Microbiologist, Institute for Microbiology and Hygiene; 3. Professor of Neurology, NeuroCure Clinical Research Centre and Centre for Stroke Research Berlin, and Attending Physician, and Neurointensivist, Department of Neurology, Charité Medical University Berlin

Abstract

Despite modern stroke treatment in dedicated stroke units and rehabilitation facilities, infection remains the most important medical complication after ischaemic stroke. Pneumonia and urinary tract infections are the most frequent post-stroke infections. Post-stroke infections not only prolong hospitalisation but also constitute a leading cause of early and long-term mortality and morbidity. They are commonly attributed to neurological sequelae such as immobilisation due to motor paralysis or dysphagia as a risk of aspiration. Recently, stroke-induced impairment of immunological competence has been described. This immunodepression syndrome promotes the development of post-stroke infection. Knowledge about risk factors for post-stroke infections, early and proper diagnosis and a deliberate decision for anti-infective treatment are of evident importance, but all of these are considered major challenges for stroke neurologists. In this article we will discuss new insights into diagnostic approaches and risk factors for post-stroke infections. Furthermore, we will focus on preventative approaches and the current treatment options.

Keywords

Ischaemic stroke, pneumonia, urinary tract infection, immunodepression, diagnostic, prevention, treatment

Disclosure: Hendrik Harms and Elke Halle have received speaker's honoraria from Bayer Vital GmbH. Andreas Meisel has received speaker's honoraria from Bayer Vital GmbH and Wyeth Pharma GmbH. A patent application on anti-infective agents and immunomodulators used for preventative therapy following an acute cerebrovascular accident has been filed to the European Patent Office (PCT/EP03/02246): patent owner Charité Universitaetsmedizin Berlin, patent inventors Andreas Meisel and Elke Halle.
Received: 20 May 2010 **Accepted:** 28 June 2010 **Citation:** *European Neurological Review*, 2010;5(1):39–43 *DOI:10.17925/ENR.2010.05.01.39*
Correspondence: Andreas Meisel, Centre of Stroke Research Berlin, Department of Neurology, Charité Universitaetsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E: andreas.meisel@charite.de

Up to 95% of patients have at least one relevant complication within the first three months after stroke.[1] Complications impair neurological outcomes[2–4] and approximately one-third of patients with ischaemic stroke die during hospitalisation due to one or more complications.[5] To minimise the impact of stroke-associated adverse events, patients should be treated in specialised units where complications are detected earlier compared with general units. In addition, treatment in stroke units improves survival by preventing life-threatening situations.[3]

However, even in specialised stroke units, stroke-associated infections remain one of the major complications in acute stroke, with frequencies between 21 and 65%.[6] The incidence of infection among stroke patients is thus significantly higher than the general prevalence of hospital-acquired infection, which ranges from 6 to 9% in all hospitalised patients.[7,8]

Bacterial pneumonia and urinary tract infection (UTI) are the predominant infections in acute stroke patients.[2,9] The incidence of UTI in acute stroke ranges between 6 and 27%, whereas the frequency of stroke-associated pneumonia (SAP) lies between 5 and 22%.[6,10–12] This compares with an average rate of pneumonia of only 3.5% in non-stroke patients treated in a geriatric hospital.[13] In the general population, the risk of UTI is between 3 and 10% per day of catheterisation.[14,15]

Diagnosis of Post-stroke Infections

Post-stroke Pneumonia

Traditionally, the diagnosis of pneumonia requires a combination of clinical assessment, radiological imaging and appropriate microbiological tests; however, a reliable diagnosis of pneumonia remains a medical challenge, even in stroke patients. Unspecific symptoms of respiratory infection are fever or hypothermia, cough, purulent secretion, dyspnoea, myalgia, arthralgia, headache and delirium; therefore, clinical examinations alone do not improve diagnostic properties. Radiological examination and microbiological tests are mandatory to establish the diagnosis of classic (bacterial) pneumonia. This is reasonable because plain chest radiography is an inexpensive test and an important initial examination in all patients with suspected pneumonia.[16] However, diagnostic properties are limited even in immobilised stroke patients.[17,18]

Computed tomography (CT) is a valuable adjunct in negative or non-diagnostic chest radiography, unresolved pneumonias and when complications are suspected.[19] However, even in current Centers for Disease Control and Prevention (CDC) guidelines, chest radiography remains the central diagnostic tool.

In stroke patients, we recommend the use of the criteria for a 'clinically defined pneumonia' (see *Table 1*) in which diagnosis is possible without further microbiological tests.

© TOUCH BRIEFINGS 2010

Table 1: Centers for Disease Control and Prevention Criteria for Clinically Defined Pneumonia

Signs/Symptoms/Laboratory	Radiology
For any patient, at least one of the following: • fever (>38ºC) • leukopenia (<4,000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3) • for adults ≥70 years of age, altered mental status with no other recognised cause	Two or more serial chest radiographs with a least one of the following: • new or progressive and persistent infiltrate • consolidation • cavitation • in patients without underlying pulmonary or cardiac diseases (e.g. respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary oedema or chronic obstructive pulmonary diseases), one definitive chest radiograph is acceptable

WBC = white blood cells. Adapted from Centers for Disease Control and Prevention, 2009.

Table 2: Centers for Disease Control and Prevention Criteria for Asymptomatic Bacteriuria

Signs/Symptoms	Laboratory
Patient has not had an indwelling urinary catheter within seven days before the first positive culture and patient has: • no fever (>38ºC) • no urgency • no frequency • no dysuria • no suprapubic tenderness	Patient has had at least two *positive* cultures, that is ≥10^5 micro-organisms/ml of urine with repeated isolation of the same micro-organisms and no more than two species of micro-organism

Table 3: Centers for Disease Control and Prevention Criteria for Symptomatic Urinary Tract Infection

Signs/Symptoms	Laboratory
Patient has at least one of the following signs: • fever (>38°C) • urgency • frequency • dysuria • suprapubic tenderness	Patient has had a positive culture, that is ≥10^5 micro-organisms/ml of urine with repeated isolation of the same micro-organisms and no more than two species of micro-organisms or at least one of the following: • positive dipstick for leukocyte esterase and/or nitrate • pyuria (urine specimen with ≥10 WBC/ml or ≥3 WBC/high-power field of unspun urine) • organisms seen on Gram stain of unspun urine • at least two urine cultures with repeated isolation of the same uropathogen (Gram-negative bacteria or *Staphylococcus saprophyticus*) with ≥10^2 micro-organisms/ml in non-voided specimens • ≤10^5 micro-organisms/ml of a single uropathogen (Gram-negative bacteria or *S. saprophyticus*) in a patient being treated with an effective antimicrobial agent for a urinary infection • physician diagnosis of a urinary tract infection • physician institutes appropriate therapy for a urinary tract infection

WBC = white blood cells. Adapted from Centers for Disease Control and Prevention, 2009.

Urinary Tract Infection

It is important to differentiate between UTI and asymptomatic bacteriuria. Asymptomatic bacteriuria (see *Table 2*) is a common phenomenon in populations with structural or functional abnormalities of the genito-urinary tract, but even healthy individuals frequently have positive urine cultures. Asymptomatic bacteriuria is seldom associated with adverse outcomes.

Symptomatic UTI has been defined by the CDC, as depicted in *Table 3*. One should note that in stroke patients clinical signs of UTI (e.g. dysuria or urgency) are of only minor diagnostic value, as stroke patients are often unconscious or dysphasic. Thus, laboratory and microbiological testing are of enhanced relevance. Interestingly, diagnosis of UTI can also be a decision of the treating physicians.

Prediction of Post-stroke Infections

Early identification of patients at high risk of post-stroke infection may promote and justify intensive monitoring and tailored anti-infective treatment.

Pneumonia

Post-stroke pneumonia is usually explained as a result of aspiration due to neurological deficits, such as impaired level of consciousness, disturbed protective reflexes[20] or dysphagia.[21] Additional risk factors for the SAP have been identified: stroke severity, stroke subtype, lesion size, mechanical ventilation, age, gender and history of diabetes.[21–24] A study by Walter et al. underlined the pivotal role of post-stroke dysphagia with a 10-fold relative risk of post-stroke pneumonia.[23] The first published scoring system to predict post-stroke pneumonia was developed including National Institutes of Health Stroke Scale (NIHSS), age, sex, mechanical ventilation and dysphagia.[25] Sellars et al. established a scoring system by identifying age ≥65 years, dysarthria, modified Rankin Scale (mRS) ≥4, Abbreviated Mental Test (AMT) <8 and dysphagia (failed water swallowing test) as independent clinical risk factors for SAP in 412 stroke patients. The presence of two or more of these risk factors carried 90.9% sensitivity and 75.6% specificity for the development of pneumonia in this study.[26] However, both scores need further refinement and prospective validation in large multicentre trials.

The impact of aspiration on the risk of post-stroke pneumonia is indisputable. However, aspiration alone is not sufficient to explain the high incidence of pneumonia in acute stroke, as about 50% of healthy subjects also aspirate pharyngeal secrets every night to a similar extent to stroke patients without developing pneumonia.[27,28] Clinical and experimental evidence suggests that acute ischaemic central nervous system (CNS) injury is associated with temporary immunodeficiency and that an impaired antibacterial host defence is an important factor for the increased susceptibility to infection after CNS injury.[6,10–12,29]

In experimental stroke models, cerebral ischaemia induces a rapid suppression of cellular immune responses in lymphatic organs – in

the lung as well as in blood. In experimental stroke, these changes in immunity precede the development of bacterial infection in the lung.[30–33] Impaired early lymphocyte responses, in particular reduced interferon gamma (IFN-γ) production by natural killer (NK) and T cells, appear to be an essential stroke-induced defect in the antibacterial defence as prevention of lymphocyte apoptosis by caspase inhibitors,[34] adoptive transfer of IFN-γ-producing lymphocytes (i.e. T and NK cells) or early treatment with recombinant IFN-γ inhibit pneumonia after experimental stroke.[30,35] Stroke-induced immunodepression is long-lasting and facilitates the development of severe pneumonia after aspiration of an otherwise harmless small dose of *Streptococcus pneumoniae* even 14 days after experimental stroke.[35]

Recent evidence from clinical studies[36–41] indicates that down-regulation of systemic cellular immune responses, including rapid decrease in peripheral blood lymphocyte counts and functional deactivation of monocytes and T-helper type 1 cells, also occurs in stroke patients. Additionally, signs of immunodepression are more prominent in patients who develop infectious complications. Collectively, these clinical data corroborate experimental findings that changes in immune responsiveness after stroke occur before the onset of infectious complications and indicate that the extent of stroke-induced immunodepression correlates with the risk of infectious complication.

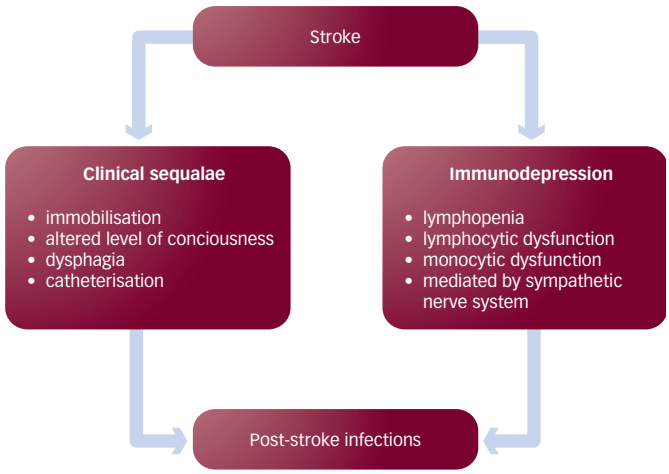
Recently, we and others described immune parameters significantly associated with infectious complications after stroke.[36,38,42,43] For example, patients with infection had significantly lower levels of the major histocompatibility class II (MHCII) molecule human leukocyte antigen-DR (HLA-DR) on monocytes at days one, three and eight than non-infected patients. Moreover, reduced monocytic HLA-DR expression at day one was a strong independent predictor of subsequent post-stroke infection.[36,41] Thus, immunological or infection parameters may be helpful predictors of post-stroke pneumonia. The current concept of post-stroke infections is shown in *Figure 1*.

Urinary Tract Infection

Several parameters are known to increase the risk of UTI after stroke including female sex, age, dependency before stroke, stroke severity (measured by NIHSS), poor cognitive function and catheterisation.[22,44] Catheterisation is a well-described risk factor for healthcare-associated UTI. Their inappropriate use may be more common in stroke patients, thereby further increasing the risk of UTI. Usually, catheterisation is a consequence of urinary dysfunction and retention, occurring in 29–58% of stroke patients.[45] Urine-storage disorder due to bladder hyper-reflexia seems to be more common after stroke.[46] Risk factors for bladder dysfunction include large infarcts and cortical involvement. In addition, aphasia, cognitive impairment and severe functional impairment are independently associated with bladder dysfunction.[47]

Only a few studies have focused on the use of Foley catheters in patients with acute stroke; therefore, frequency of use remains unclear. However, clinical characteristics of stroke patients may promote catheter placement. Disturbance of consciousness and dysphasia impaired the ability to communicate the need to urinate. In addition, the high incidence of bladder dysfunction will increase the probability of being catheterised. Immobilisation due to motor dysfunction will complicate transfer to the toilet and even hamper the use of helpful devices, such as urinals or bedpans. In addition, the above-mentioned immunodepressive state induced by the acute CNS lesion may lead not only to chest infections but also to UTI.

Figure 1: Current Concept of Post-stroke Infections



Prevention of Post-stroke Infections

Pneumonia

As dysphagia is the most important risk factor for post-stroke pneumonia, several approaches aim at minimising the risk of aspiration. One well-known drawback is the lack of reliable diagnostic screening methods to identify patients at high risk of aspiration. Clinical bedside assessments have been shown to miss up to 40% of those patients who aspirate ('silent aspiration').[47–49] Videofluoroscopy (VFS) can be considered the gold standard in diagnosing dysphagia with aspirations (silent or not) because of its ability to study the entire process of swallowing.[49] Nevertheless, this examination requires patient co-operation and a sitting posture, so it cannot be proposed for all patients in the early period after stroke.

However, screening for dysphagia is effective to prevent post-stroke pneumonia. Using a formal dysphagia screening protocol decreases the risk of pneumonia in patients hospitalised for ischaemic stroke by three-fold.[50] In order to reduce the risk of aspiration, dysphagia is usually managed by placement of a nasogastric tube. Percutaneous endoscopic gastrostomy (PEG) is applied to patients who remain unable to swallow in the long term. Although a nasogastric tube is easy to insert, it is uncomfortable and can be easily dislodged, leading to treatment failure and aspiration. PEG placement is an invasive procedure and can be complicated by peritonitis or bowel perforation.[51] The Feed Or Ordinary Diet (FOOD) trials demonstrated that early enteral tube feeding might reduce case fatality compared with no tube feeding for more than seven days after stroke onset. However, the overall increase in survival was associated with an increased proportion of survivors with poor outcome. Compared with nasogastric tube feeding, early PEG tube feeding might be associated with poorer outcome and should be avoided in stroke patients. Furthermore, there were no significant differences between groups in the frequency of pneumonia, suggesting that early tube feeding does not prevent or favour infection rates.[52]

Table 3: Clinical Risk Factors for Post-stroke Pneumonia

>65 years of age	Non-lacunar basal ganglia infarction
Stroke severity	Other infection at stroke onset
Dysphagia	Mechanical ventilation
Dysarthria/dysphasia	Male gender
Dementia	Infarct volume

Sources: Walter et al., 2007,[23] Kwon et al., 2006,[25] Sellars et al., 2007[26] and Minnerup, 2010.[69]

Table 4: Anti-infective Treatment of Post-stroke Pneumonia

Drug	Daily Dosage
Without Risk Factors for Higher-level Resistant Bacteria	
Ampicillin/sulbactam	3x3g
Cefuroxime	3x1.5g
Ceftriaxone	1x2g
Levofloxacin	2x500mg
Moxifloxacin	1x400mg
With Risk Factors for Higher-level Resistant Bacteria	
Ceftazidime	3x2g
Combined with gentamicine	5–7mg/kg bodyweight

Table 5: Treatment of Symptomatic Urinary Tract Infection

Drug	Dosage
Trimethoprim/sulfamethoxazole	2x800/160mg
Ampicillin/sublactam	3x3g
Ceftriaxone	1x2g
Ciprofloxacin	2x500mg
Levofloxacin	2x500mg

Another practical approach to prevent post-stroke pneumonia is anti-infective prophylaxis. In a rodent stroke model, moxifloxacin given immediately or 12 hours after middle cerebral artery occlusion prevented infection and fever, significantly reduced mortality and improved neurological outcome.[53] Over the last few years, three heterogeneous randomised clinical trials have tested the efficacy of antibiotic prophylaxis in acute stroke to prevent post-stroke infection.[36,54,55] Differences in inclusion criteria, infection criteria, type of intervention and outcome measures may have led to conflicting results. Although a meta-analysis demonstrated that antibacterial prophylaxis reduced the occurrence of post-stroke infection from 38 to 24% (odds ratio [OR] 0.44, 95% confidence interval [CI] 0.23–0.86),[56] the beneficial effect on stroke outcome remains an open matter and has to be evaluated in future trials.

Urinary Tract Infection

As the use of Foley catheters increases the risk of UTI after stroke, the limited use of catheterisation may prevent UTI after stroke. Educational interventions can influence the inappropriate use of Foley catheters[57,58] and thus dramatically reduce the frequency of UTI.[58] Antiseptic-coated catheters have also been studied in the prevention of UTI. Only small clinical trials have shown that silver-oxide-coated catheters may reduce asymptomatic bacteriuria. However, these trials did not evaluate the efficacy of silver-oxide-coated catheters in symptomatic UTI.[59] Antibiotic-impregnated catheters or condom catheters may reduce the frequency of asymptomatic bacteriuria.[59,60] Thus, the general use of antiseptic-coated or condom catheters can not be recommended.

Antimicrobial prophylaxis may reduce the risk of stroke-associated UTI. However, the current urological guidelines strongly discourage prophylactic antibacterial treatment due to the lack of convincing evidence that it prevents bacteriuria and the risk of adverse events and antimicrobial resistance.[61]

Treatment of Post-stroke Infections

Current guidelines for stroke treatment recommend early diagnosis and antibacterial treatment in cases of suspected infection.[62,63] Basically, anti-infective treatment of post-stroke infection follows current treatment guidelines of hospital-acquired (bacterial) pneumonia (HAP) or UTI, respectively. After initiating empirical antibacterial treatment, the isolation of pathogens from relevant species should be the main diagnostic focus. Thereafter, treatment should be adapted to results of resistance testing.

Pneumonia

Post-stroke pneumonia usually occurs within the first three to five days after hospitalisation[36,54,55] and thus can be considered as early-onset HAP. Early-onset HAP is primarily attributed to Gram-negative bacteria, such as *Haemophilus influenzae*, and Gram-positive bacteria such as methicillin (meticillin)-sensitive *Staphylococcus aureus* (MSSA) and *S. pneumoniae*. Late-onset nosocomial pneumonia is usually attributed to higher-level antibiotic-resistant Gram-negative bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* spp.) and Gram-positive bacteria (e.g. methicillin-resistant *S. aureus* [MRSA]). This classification leads to different strategies for empirical antimicrobial treatment: monotherapy with narrow-spectrum antibiotics for the treatment of early-onset pneumonia but broad-spectrum therapy for *Pseudomonas* spp. or MRSA with late-onset infection. However, this dichotomised concept is currently under discussion.[64,65] Importantly, empirical antibacterial treatment should follow local information about antimicrobial resistance. It is strongly recommended to stratify the risk of higher-level resistant bacteria using the following risk factors: inhabitant of healthcare facilities, medical co-morbidity (chronic heart disease, cirrhosis, renal insufficiency) and preceding anti-infective treatment.

Patients with low risk of higher-level resistant bacteria should be treated with antibacterial monotherapy. Aminopenicillin/β-lactamase inhibitors (BI) (e.g. amoxicilline/sulbactam), cephalosporins group II/III (e.g. cefuroxime/ceftriaxone) or fluorochinolones (e.g. moxifloxacin/levofloxacin) are recommended in these cases.

High-risk patients should be treated with a combination of cephalosporines group IIIb (e.g. ceftazidime) and aminoglycosides (e.g. gentamicine). Three to five days after clinical improvement, the antibacterial treatment should be terminated. In total, the treatment period should not exceed 10 to 14 days (see *Table 4*).

Urinary Tract Infection

The most common pathogen in UTI remains *Escherichia coli* (55–80%). In about 5–10% of cases, other *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella* spp., can be isolated. Occasionally, *Staphylococcus saprophyticus* are isolated.[66–68] Knowledge of the antimicrobial susceptibility profile of uropathogens causing uncomplicated UTI in the community should guide therapeutic

decisions. However, the resistance pattern of *E. coli* strains and other pathogens causing UTI may vary considerably between European regions and countries, so that no general recommendations are suitable throughout Europe.

The following antimicrobials can be considered (see *Table 5*): trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones (e.g. ciprofloxacin, levofloxacin,) and β-lactams (e.g. ampicillin/sulbactam, ceftriaxone). Treatment duration should not exceed seven days.

Conclusion and Perspectives

Even in dedicated stroke units with regular quality management protocols, post-stroke infections remain relevant complications that can be prevented and treated. Although their effect on long-term outcome remains an open issue, it is highly probable that post-stroke infections have a negative impact on mortality and neurological status. In the next few years, several predictive tools (e.g. clinical scores, blood-borne biomarkers) will be developed and validated. Thus, patients at risk will be identified early and reliably. Additionally, pre-emptive and biomarker-guided anti-infective treatment approaches will be tested to improve neurological outcome after stroke. ■

Hendrik Harms is a Clinical Scientist at the Centre for Stroke Research Berlin and an Attending Neurologist in the Department of Neurology at the Charité Medical University Berlin. His scientific and clinical focus is ischaemic stroke and its implication for immune functions, and the pathogenesis of autoimmune neuropathies.

Elke Halle is a Clinical Scientist and Attending Microbiologist at the Institute for Microbiology and Hygiene. A clinical microbiologist and an expert on antibiotical therapies, she has been involved in the conception of the German S3 guidelines for community-acquired pneumonia. Over the past 10 years she has collaborated with Drs Meisel and Harms in the conception and investigation of preventative anti-infective therapy as a treatment strategy in stroke.

Andreas Meisel is a Professor of Neurology at the NeuroCure Clinical Research Centre and the Centre for Stroke Research Berlin and an Attending Physician and Neurointensivist in the Department of Neurology at the Charité Medical University Berlin, where his work is mainly focused on stroke and myasthenia gravis. His group is active in the field of experimental and clinical stroke research, dissecting mechanisms and functional relevance of stroke-induced immunodepression and endogenous neuroprotection and brain repair.

1. Davenport RJ, Dennis MS, Wellwood I, Warlow CP, *Stroke*, 1996;27(3):415–20.
2. Langhorne P, Stott DJ, Robertson L, et al., *Stroke*, 2000;31(6):1223–9.
3. Langhorne P, Williams BO, Gilchrist W, Howie K, *Lancet*, 1993;342(8868):395–8.
4. Tong X, Kuklina EV, Gillespie C, George MG, *Stroke*, 2010;41(5):980–86.
5. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, et al., *Arch Intern Med*, 2004;164(16):1761–8.
6. Meisel C, Schwab JM, Prass K, et al., *Nat Rev Neurosci*, 2005;6(10):775–86.
7. Emmerson AM, Enstone JE, Griffin M, et al., *J Hosp Infect*, 1996;32(3):175–90.
8. Andersen BM, Ringertz SH, Gullord TP, et al., *J Hosp Infect*, 2000;44(3):214–23.
9. Hilker R, Poetter C, Findeisen N, et al., *Stroke*, 2003;34(4):975–81.
10. Dirnagl U, Klehmet J, Braun JS, et al., *Stroke*, 2007;38(Suppl. 2):770–73.
11. Chamorro A, Urra X, Planas AM, *Stroke*, 2007;38(3):1097–1103.
12. Emsley HC, Hopkins SJ, *Lancet Neurol*, 2008;7(4):341–53.
13. Rothan-Tondeur M, Meaume S, Girard L, et al., *J Am Geriatr Soc*, 2003; 51(7):997–1001.
14. Maki DG, Tambyah PA, *Emerg Infect Dis*, 2001;7(2):342–7.
15. Gould C, Allen-Bridson K, Horan T, *Clin Infect Dis*, 2009;49(8):1288–9.
16. Bartlett JG, Dowell SF, Mandell LA, et al., *Clin Infect Dis*, 2000;31:347–82.
17. Melbye H, Dale K, *Acta Radiol*, 1992;33(1):79–81.
18. Young M, Marrie TJ, *Arch Intern Med*, 1994;154(23):2729–32.
19. Niederman MS, Mandell LA, Anzneto A, et al., *Am J Respir Crit Care Med*, 2001;163:1730–54.
20. Nakajoh K, Nakagawa T, Sekizawa K, et al., *J Intern Med*, 2000;247(1):39–42.
21. Hilker R, Poetter C, Findeisen N, et al., *Stroke*, 2003;34(4):975–81.
22. Aslanyan S, Weir CJ, Diener HC, et al., *Eur J Neurol*, 2004;11:49–53.
23. Walter U, Knoblich R, Steinhagen V, et al., *J Neurol*, 2007;254(10):1323–9.
24. Hug A, Dalpke A, Wieczorek N, et al., *Stroke*, 2009;40(10):3226–32.
25. Kwon HM, Jeong SW, Lee SH, Yoon BW, *Am J Infect Control*, 2006;34(2):64–8.
26. Sellars C, Bowie L, Bagg J, et al., *Stroke*, 2007;38(8):2284–91.
27. Huxley EJ, Viroslav J, Gray WR, Pierce AK, *Am J Med*, 1978;64:564–68.
28. Gleeson K, Eggli DF, Maxwell SL, *Chest*, 1997;111:1266–72.
29. Dziedzic T, Slowik A, Szczudlik A, *Crit Care*, 2004;8(4):266–70.
30. Prass K, Meisel C, Hoflich C, et al., *J Exp Med*, 2003;198(5):725–36.
31. Offner H, Subramanian S, Parker SM, et al., *J Immunol*, 2006;176(11):6523–31.
32. Meisel C, Prass K, Braun J, et al., *Stroke*, 2004; 35(1):2–6.
33. Schulte-Herbruggen O, Klehmet J, Quarcoo D, et al., *Neuroimmunomodulation*, 2006;13(1):13–18.
34. Braun JS, Prass K, Dirnagl U, et al., *Exp Neurol*, 2007;206(2):183–91.
35. Prass K, Braun JS, Dirnagl U, et al., *Stroke*, 2006;37(10):2607–12.
36. Harms H, Prass K, Meisel C, et al., *PLoS One*, 2008;14;3(5):e2158.
37. Haeusler KG, Schmidt WU, Fohring F, et al., *Cerebrovasc Dis*, 2008;25(1–2):50–58.
38. Chamorro A, Amaro S, Vargas M, et al., *J Neurol Neurosurg Psychiatry*, 2006; 77(11):1279–81.
39. Chamorro A, Amaro S, Vargas M, et al., *J Neurol Sci*, 2007;252(1):29–35.
40. Czlonkowska A, Cyrta B, Korlak J, *J Neurol Sci*, 1979;43(3):455–64.
41. Vogelgesang A, Grunwald U, Langner S, et al., *Stroke*, 2008;39(1):237–41.
42. Klehmet J, Harms H, Richter M, et al., *Neuroscience*, 2009;158(3):1184–93.
43. Urra X, Cervera A, Obach V, et al., *Stroke*, 2009;40(4):1262–8.
44. Stott DJ, Falconer A, Miller H, et al., *QJM*, 2009;102(4):243–9.
45. Kong KH, Young S, *Arch Phys Med Rehabil*, 2000;81:1464–7.
46. Ersoz M, Tunc H, Akyuz M, Ozel S, *Cerebrovasc Dis*, 2005;20:395–9.
47. Linden P, Siebens A, *Arch Phys Med Rehabil*, 1983;64:281–4.
48. Splaingard M, Hutchins B, Sulton L, Chaudhuri G, *Arch Phys Med Rehabil*, 1988;69:637–40.
49. Perry L, Love C, *Dysphagia*, 2001;16:7–18.
50. Hinchey JA, Shephard T, Furie K, et al., *Stroke*, 2005;36(9):1972–6.
51. Wiggam MI, Webster A, Dennis MS, *Age Ageing*, 2001;30(Suppl. 2):72.
52. Dennis MS, Lewis SC, Warlow C, *Lancet*, 2005;365(9461):764–7.
53. Meisel C, Prass K, Braun J, et al., *Stroke*, 2004;35(1):2–6.
54. Chamorro A, Horcajada JP, Obach V, et al., *Stroke*, 2005;36(7):1495–1500.
55. Schwarz S, Al-Shajlawi F, Sick C, et al., *Stroke*, 2008;39(4):1220–27.
56. van de Beek D, Wijdicks EF, Vermeij FH, et al., *Arch Neurol*, 2009;66(9):1076–81.
57. Gokula RM, Smith MA, Hickner J, *Am J Infect Control*, 2007;35:589–93.
58. Topal J, Conklin S, Camp K, et al., *Am J Med Qual*, 2005;20:121–6.
59. Schumm K, Lam TB, *Cochrane Database Syst Rev*, 2008;2:CD004013.
60. Saint S, Kaufman SR, Rogers MA, et al., *J Am Geriatr Soc*, 2006;54:1055–61.
61. Hooton TM, Bradley SF, Cardenas DD, et al., *Clin Infect Dis*, 2010;50(5):625–63.
62. Adams HP Jr, del Zoppo G, Alberts MJ, et al., *Stroke*, 2007;38(5):1655–1711.
63. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee, *Cerebrovasc Dis*, 2008;25(5):457–507.
64. Gastmeier P, Sohr D, Geffers C, et al., *Antimicrob Agents Chemother*, 2009;53(7):2714–18.
65. Verhamme KM, De Coster W, De Roo L, et al., *Infect Control Hosp Epidemiol*, 2007;28(4):389–97.
66. Winstanley TG, Limb DI, Eggington R, Hancock F, *J Antimicrob Chemother*, 1997;40(4):591–4.
67. Bonadio M, Meini M, Spitaleri P, Gigli C, *Eur Urol*, 2001;40:439–45.
68. Zhanel GG, Hisanaga TL, Laing NM, et al., *Int J Antimicrob Agents*, 2005;26(5):380–88.
69. Minnerup J, et al., *J Neurol Neurosurg Psychiatry*, 2010;81(2):198–202.