Intern Emerg Med
DOI 10.1007/s11739-016-1462-2

IM - ORIGINAL

Prophylactic antibiotic treatment in severe acute ischemic stroke: the *A*ntimicrobial chemop*R*rophylaxis for *I*schemic *ST*rok*E* *I*n Mace*D*on*I*a–Thrace *S*tudy (ARISTEIDIS)

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Received: 2 February 2016 / Accepted: 6 May 2016

Abstract Infections represent a leading cause of mortality in patients with acute ischemic stroke, but it is unclear whether prophylactic antibiotic treatment improves the outcome. We aimed to evaluate the effects of this treatment on infection incidence and short-term mortality. This was a pragmatic, prospective multicenter real-world analysis of previously independent consecutive patients with acute ischemic stroke who were >18 years, and who had at admission National Institutes of Health Stroke Scale (NIHSS) >11. Patients with infection at admission or during the preceding month, with axillary temperature at admission >37 °C, with chronic inflammatory diseases or under treatment with corticosteroids were excluded from the study. Among 110 patients (44.5 % males, 80.2 ± 6.8 years), 31 (28.2 %) received prophylactic antibiotic treatment, mostly cefuroxime ($n = 21$). Prophylactic antibiotic treatment was administered to 51.4 % of patients who developed infection, and to 16.4 % of patients who did not ($p < 0.001$). Independent predictors of infection were NIHSS at admission [relative risk (RR) 1.16, 95 % confidence interval (CI) 1.08–1.26, $p < 0.001$] and prophylactic antibiotic treatment (RR 5.84, 95 % CI 2.03–16.79, $p < 0.001$). The proportion of patients who received prophylactic antibiotic treatment did not differ between patients who died during hospitalization and those discharged, or between patients who died during hospitalization or during follow-up and those who were alive 3 months after discharge. Prophylactic administration of antibiotics in patients with severe acute ischemic stroke is associated with an increased risk of infection during hospitalization, and does not affect short-term mortality risk.

Keywords Antibiotic prophylaxis · Acute ischemic stroke · Pneumonia · Urinary tract infection · Decubitus ulcer infection · Outcome · Stroke-related infection

Under the auspices of the Internal Medicine Society of Northern Greece.

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Introduction

Infections develop in more than one-third of patients hospitalized for acute ischemic stroke [1–5]. Aspiration-associated aspiration, urinary tract infections due to placement of indwelling urinary catheters and decubitus ulcer infections are the most common infections in these patients [5–7]. Older patients and those with more severe stroke have the highest risk for infections [1, 8]. Infections, and

Published online: 23 May 2016

particularly pneumonia, represent a leading cause of mortality in patients with acute stroke, and are also associated with worse functional outcomes [2–4, 8].

Given the high incidence of infections in patients with acute ischemic stroke and the association between infection and adverse outcome, several studies evaluated whether prophylactic administration of antibiotics might reduce the risk of infection and improve the outcome of these patients [9–14]. However, these studies reported conflicting results. In one study, prophylactic administration of antibiotics reduces the risk of infections, and is associated with better functional outcome [11]. In contrast, the incidence of infection is not affected by antibiotic prophylaxis in other studies [10–14], or is even increased in an early report [14], whereas the functional outcome is either the same [12], or worse in those who receive antibiotic prophylaxis [13]. Accordingly, current guidelines do not recommend the use of prophylactic antibiotics in patients with acute stroke [15].

The aim of the present study was to evaluate whether prophylactic administration of antibiotics in patients admitted with severe acute ischemic stroke affects the incidence of infection during hospitalization and the in-hospital and short-term mortality.

Patients and methods

This was a pragmatic, prospective multicenter real-world analysis of previously independent [defined as modified Rankin scale (mRS) prior to stroke <2] consecutive patients with acute ischemic stroke who were >18 years, who had at admission National Institutes of Health Stroke Scale (NIHSS) >11 and a modified Rankin Scale (mRS) ≥3. Patients with infection at admission or during the preceding month, with axillary temperature at admission >37 °C, with chronic inflammatory diseases or under treatment with corticosteroids were excluded from the study. The presence of infection on admission was assessed by taking into consideration findings which could be suggestive of infection and could be identified during clinical examination (e.g., dyspnoea, tachypnoea, fever, fine crackles at auscultation of the thorax, and dysuria), laboratory examinations (e.g., C-reactive protein, leukocyte count, and urine examination), and imaging techniques (e.g., chest X-ray). The study was performed under the auspices of the Internal Medicine Society of Northern Greece.

At admission, demographic data (age and gender), history of cardiovascular risk factors [hypertension, type 2 diabetes mellitus (T2DM), atrial fibrillation, smoking, alcohol intake, and family history of premature cardiovascular disease (CVD)], history of concomitant CVD (coronary heart disease (CHD) or previous ischemic stroke), and pharmacological treatment were recorded. Anthropometric parameters (weight and height) and systolic and diastolic blood pressure were also measured.

Routine laboratory investigations were performed after overnight fasting on the first day after admission, and included serum levels of glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides (TG), creatinine, and uric acid. Low-density lipoprotein cholesterol levels were calculated using Friedewald's formula [16]. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation [17]. Chronic kidney disease was defined as estimated GFR <60 ml/min/1.73 m^2. All patients underwent brain computed tomography at admission, and a second brain computed tomography was performed if clinically indicated.

Clinical decisions about the administration of prophylactic antibiotic treatment, the selection of antibiotic, the timing of initiation, and the duration of treatment were made by the treating physicians based on parameters such as stroke severity, presence of dysphagia, early signs of impending infection, and presence of a urinary catheter. Pneumonia was diagnosed if a patient had two or more serial chest radiographs with at least one of the following: new or progressive and persistent infiltrate, consolidation or cavitation; and also had at least 1 of the following: (a) fever (>38 °C) with no other recognized cause, (b) white blood cells ≥12,000/mm^3 or <4000/mm^3, or (c) in patients >70 year-old, altered mental status with no other recognized cause; and also had at least two of the following: (a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, (b) new onset or worsening cough, or dyspnea, or tachypnea, (c) rales or bronchial breath sounds, or (d) worsening gas exchange [e.g., O_2 desaturations (e.g., PaO_2/FiO_2 ≤240)], increased oxygen requirements [18]. Urinary tract infection was diagnosed if a patient developed at least one of the following signs or symptoms with no other recognized cause: (a) fever (>38 °C), (b) urgency, (c) frequency, (d) dysuria, or (e) suprapubic tenderness, and the patient had a positive urine culture (i.e., ≥10^5 microorganisms per cc of urine with no more than two species of microorganisms) [18]. Decubitus ulcer infection was diagnosed if a patient developed at least two of the following signs or symptoms with no other recognized cause: (a) redness, (b) tenderness, or (c) swelling of decubitus wound edges, and at least one of the following: (a) microorganisms cultured from properly collected fluid or tissue from the ulcer or (b) microorganisms cultured from blood [18]. All patients were systemically evaluated for development of any of these infections during their hospitalization by means of physical

examination, laboratory investigation, blood, urine, and decubitus ulcer culture, and imaging.

At 3 months after discharge, patients or their proxy were contacted by phone and the mRS, and the occurrence and cause of death were recorded.

Statistical analysis

All data were analyzed with the statistical package SPSS (version 17.0; SPSS, Chicago, IL, USA). Data are presented as percentages for categorical variables and as mean and standard deviation or as median and range for continuous variables. Differences in categorical variables between groups were assessed with the Chi-squared test. Differences in continuous variables between groups were assessed with the independent samples t test. Binary logistic regression analysis was used to identify independent predictors of in-hospital infection and in-hospital and 3-month mortality. In all cases, a two-tailed $p < 0.05$ was considered significant.

Results

Among 110 patients (44.5 % males, 80.2 ± 6.8 years), 31 (28.2 %) received prophylactic antibiotic treatment, mostly cefuroxime ($n = 21$; other antibiotics administered included ampicillin/sulbactam ($n = 5$), piperacillin/tazobactam ($n = 3$), amoxicillin/clavulanate ($n = 1$), and cefoxitin ($n = 1$). Prophylactic antibiotic treatment was started during the first, second, and third day of hospitalization in 19, 8, and 4 patients, respectively, and was administered for a median of 5 days (range 2–13 days). Differences between patients who received prophylactic antibiotic treatment and those who did not are shown in Table 1. The former had a higher prevalence of T2DM ($p < 0.001$) and longer duration of T2DM ($p < 0.05$), higher prevalence of CHD ($p < 0.05$), higher body mass index ($p < 0.05$), higher TG and glucose levels ($p < 0.001$ and $p < 0.05$, respectively), and higher mRS ($p < 0.001$) than the latter. Patients' characteristics at admission are summarized in Table 2.

Table 1 Characteristics of patients who received prophylactic antibiotic treatment and those who did not

Patient characteristics	Patients who received prophylactic antibiotic treatment ($n = 31$)	Patients who did not receive prophylactic antibiotic treatment ($n = 79$)	p
Age (years)	79.5 ± 5.5	80.4 ± 7.2	NS
Males (%)	38.7	46.8	NS
Hypertension (%)	87.1	78.5	NS
Type 2 diabetes mellitus (%)	45.2	12.7	<0.001
Duration of type 2 diabetes mellitus (years)	13.4 ± 5.7	6.9 ± 5.7	<0.05
Atrial fibrillation (%)	38.7	43.0	NS
Smoking (current/past, %)	3.2/25.8	12.7/24.1	NS
Package-years	59 ± 37	40 ± 27	NS
Alcohol intake (units/week)	3.3 ± 1.1	10.1 ± 11.7	NS
Family history of cardiovascular disease (%)	45.2	26.6	NS
Coronary heart disease (%)	38.7	17.7	<0.05
Previous ischemic stroke (%)	35.5	27.8	NS
Chronic kidney disease (%)	20.7	39.5	NS
Overweight/obese (%)	16.1/45.2	25.3/57.3	NS
Body mass index (kg/m^2)	29.1 ± 3.9	27.1 ± 3.6	<0.05
Systolic blood pressure (mmHg)	165 ± 23	154 ± 26	NS
Diastolic blood pressure (mmHg)	86 ± 10	84 ± 15	NS
Glucose (mg/dl)	163 ± 72	131 ± 34	<0.05
Low-density lipoprotein cholesterol (mg/dl)	137 ± 46	126 ± 43	NS
High-density lipoprotein cholesterol (mg/dl)	43 ± 12	48 ± 16	NS
Triglycerides (mg/dl)	153 ± 55	115 ± 47	<0.001
Uric acid (mg/dl)	5.5 ± 2.1	5.5 ± 1.6	NS
Estimated glomerular filtration rate (ml/min/1.73 m^2)	72 ± 19	68 ± 23	NS
National Institutes of Health Stroke Scale score	19.2 ± 6.8	18.9 ± 6.5	NS
Modified Rankin Scale score (3/4/5) (%)	3.2/41.9/54.8	40.5/20.3/39.2	<0.001

Table 2 Patient characteristics at admission

Patient characteristics	
Age (years)	80.2 ± 6.8
Males (%)	44.5
Hypertension (%)	80.9
Type 2 diabetes mellitus (%)	21.8
Duration of type 2 diabetes mellitus (years)	10.5 ± 6.5
Atrial fibrillation (%)	41.8
Smoking (current/past, %)	10.0/24.5
Package-years	44.1 ± 30.5
Alcohol intake (units/week)	8.9 ± 10.8
Family history of cardiovascular disease (%)	31.8
Coronary heart disease (%)	23.6
Previous ischemic stroke (%)	30.0
Chronic kidney disease (%)	34.3
Overweight/obese (%)	53.8/23.6
Body mass index (kg/m^2)	27.7 ± 3.8
Systolic blood pressure (mmHg)	157 ± 25
Diastolic blood pressure (mmHg)	85 ± 14
Glucose (mg/dl)	140 ± 50
Low-density lipoprotein cholesterol (mg/dl)	129 ± 44
High-density lipoprotein cholesterol (mg/dl)	47 ± 15
Triglycerides (mg/dl)	126 ± 52
Uric acid (mg/dl)	5.5 ± 1.7
Estimated glomerular filtration rate (ml/min/1.73 m^2)	69 ± 22
National Institutes of Health Stroke Scale score	18.9 ± 6.6
Modified Rankin Scale score (3/4/5) (%)	30.0/26.4/43.6

During hospitalization, 37 patients developed an infection (33.6 % of the study population). The most common infections were pneumonia ($n = 17$) and urinary tract infection ($n = 15$); five patients developed decubitus ulcer infection. Prophylactic antibiotic treatment was administered to 51.4 % of patients who developed an infection, and to 16.4 % of patients who did not develop an infection ($p < 0.001$). Patients who developed an infection had higher NIHSS at admission than those who did not develop an infection (22.7 ± 7.9 and 17.1 ± 4.9, respectively; $p < 0.001$), and also had more adverse mRS at admission (i.e., the proportion of patients with mRS of 3, 4, and 5, respectively, was 13.5, 13.5, and 73.0 % in the former and 38.4, 32.9, and 28.8 % in the latter; $p < 0.001$). In binary logistic regression analysis, independent predictors of infection were NIHSS at admission [relative risk (RR) 1.16, 95 % confidence interval (CI) 1.08–1.26, $p < 0.001$] and prophylactic antibiotic treatment (RR 5.84, 95 % CI 2.03–16.79, $p < 0.001$).

Twenty-three patients died during hospitalization (20.9 % of the study population). The most common causes of death were stroke ($n = 11$) and pneumonia ($n = 10$); two patients died of respiratory failure and myocardial infarction, respectively. At admission, patients who died during hospitalization had higher HDL-C levels than those who were discharged (56 ± 21 and 45 ± 12, respectively; $p < 0.05$), higher serum glucose levels (163 ± 66 and 134 ± 43, respectively; $p < 0.01$), higher NIHSS (25.1 ± 8.0 and 17.4 ± 5.1, respectively; $p < 0.001$), and more adverse mRS (i.e., the proportion of patients with mRS of 3, 4 and 5, respectively, was 0.0, 4.3, and 95.7 % in the former and 37.9, 32.2, and 29.9 % in the latter; $p < 0.001$). The proportion of patients who received prophylactic antibiotic treatment did not differ between patients who died during hospitalization and those who were discharged (21.7 and 29.9 %, respectively; $p =$ NS). In binary logistic regression analysis, independent predictors of in-hospital mortality were NIHSS at admission (RR 1.19, 95 % CI 1.09–1.30, $p < 0.001$) and HDL-C levels at admission (RR 1.05, 95 % CI 1.01–1.09, $p < 0.05$).

During the 3 months of follow-up, seven patients died (i.e., 8.0 % of patients who were discharged from the hospital). Causes of death included recurrent ischemic stroke ($n = 3$), myocardial infarction ($n = 2$), and pneumonia ($n = 2$). Patients who died during hospitalization or during follow-up had higher serum glucose levels at admission than those who were alive 3 months after discharge (157 ± 61 and 134 ± 43, respectively; $p < 0.05$),

higher NIHSS (23.9 ± 8.3 and 17.1 ± 4.7, respectively; $p < 0.001$), and more adverse mRS (i.e., the proportion of patients with mRS of 3, 4, and 5, respectively, was 3.3, 6.7, and 90.0 % in the former and 40.0, 33.8, and 26.3 % in the latter; $p < 0.001$). The proportion of patients who received prophylactic antibiotic treatment did not differ between patients who died during hospitalization or during follow-up and those who were alive 3 months after discharge (26.7 and 28.8 %, respectively; $p =$ NS). In binary logistic regression analysis, independent predictors of mortality during hospitalization or during follow-up were NIHSS at admission (RR 1.11, 95 % CI 1.02–1.21, $p < 0.05$) and mRS at admission (mRS 5 vs. 3, RR 26.27, 95 % CI 3.22–214.66, $p < 0.005$; mRS 4 vs. 3, RR 2.20, 95 % CI 0.19–26.01, $p =$ NS).

Discussion

The main finding of the present study is that prophylactic treatment with antibiotics in patients with severe acute ischemic stroke is associated with an increased incidence of infections during hospitalization. Moreover, this strategy does not affect in-hospital or 3-month mortality in this population.

In the present study, patients who received prophylactic treatment with antibiotics, mostly cefuroxime, more frequently developed an infection than patients who did not receive antibiotics before a documented infection. This could perhaps be attributed to selection bias, i.e., patients being at higher risk of infection or with early signs of impending infection were prescribed antibiotics. Still, there are limited data on the role of antibiotic prophylaxis in patients with acute ischemic stroke. An early study ($n = 106$) also reports that prophylactic administration of either ampicillin or penicillin G is associated with an increased risk for infection [14]. In two more recent randomized, placebo-controlled studies ($n = 136$ and $n = 80$ patients with acute ischemic stroke), prophylaxis with levofloxacin or moxifloxacin has no effect on the incidence of infections [12, 13]. In contrast, a small pilot study ($n = 60$) reports that prophylactic administration of mezlocillin plus sulbactam reduces the risk of infection compared with placebo [11]. However, almost all patients in the placebo group in the latter study developed infection (27/30), suggesting that the criteria used to define infection might have been too broad [11]. Also, the incidence of infection was a secondary outcome of the study, which primarily aimed at evaluating the effects of prophylactic antibiosis on the incidence, height, and duration of fever [11]. Therefore, our findings further support the existing limited data on the lack of efficacy of prophylactic antibiotic treatment in reducing the risk of infections in patients with acute ischemic stroke, and also suggest the potential of harm.

In the present study, prophylactic treatment with antibiotics has no effect on either in-hospital mortality or on mortality at 3 months after discharge. Similar results are reported in a recent study that evaluated the prophylactic administration of moxifloxacin [12]. On the other hand, a randomized, placebo-controlled trial reports a worse functional outcome and a non-significant increase in mortality (24 vs. 13 %, $p = 0.12$) at 3 months in patients with acute stroke who receive prophylaxis with levofloxacin [13]. In contrast, a smaller, randomized, placebo-controlled study reports a better functional outcome in patients with acute stroke who receive prophylaxis with mezlocillin plus sulbactam [11]. However, the latter study was not designed to evaluate the effects of prophylactic antibiotic treatment on functional outcome, and other predictors of functional outcome might have not been taken into consideration [11]. Notably, previous studies that evaluated the role of prophylactic administration of antibiotics in patients with acute ischemic stroke report considerably lower mortality rates than in the present study (0–8 vs. 20.9 %), possibly because, they included less severely ill patients [11–13]. This implies the possibility of selection bias, since antibiotics are expected to be less protective in patients with very high mortality risk [19]. Indeed, our findings suggest that antibiotic prophylaxis does not affect mortality risk in patients with severe acute ischemic stroke.

Limitations of the study include the relatively low number of patients—and particularly those who received antibiotic prophylaxis—the fact that the investigator who adjudicated the presence of infection was not blinded to antibiotics use, as well as the inherent limitations of any real-world observational study like selection and registration bias. On the other hand, strengths of the study include its multicenter design and the rigorous approach to detect infection at admission and, therefore, exclude such patients.

In conclusion, our study suggests that prophylactic administration of antibiotics might be associated with an increased risk of infection during hospitalization in patients admitted with severe acute ischemic stroke. Moreover, this treatment does not affect mortality risk during hospitalization or during short-term follow-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all study participants.

References

1. Indredavik B, Rohweder G, Naalsund E, Lydersen S (2008) Medical complications in a comprehensive stroke unit and an early supported discharge service. Stroke 39:414–420
2. Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR, GAIN International Steering Committee and Investigators (2004) Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol 11:49–53
3. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP (2011) In-hospital medical complications, length of stay, and mortality among stroke unit patients. Stroke 42:3214–3218
4. Rohweder G, Ellekjær H, Salvesen Ø, Naalsund E, Indredavik B (2015) Functional outcome after common poststroke complications occurring in the first 90 days. Stroke 46:65–70
5. Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM (2013) Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis 35:430–443
6. Ionita CC, Siddiqui AH, Levy EI, Hopkins LN, Snyder KV, Gibbons KJ (2011) Acute ischemic stroke and infections. J Stroke Cerebrovasc Dis 20:1–9
7. Poisson SN, Johnston SC, Josephson SA (2010) Urinary tract infections complicating stroke: mechanisms, consequences, and possible solutions. Stroke 41:e180–e184
8. Zhang X, Wang F, Zhang Y, Ge Z (2012) Risk factors for developing pneumonia in patients with diabetes mellitus following acute ischaemic stroke. J Int Med Res 40:1860–1865
9. Kalra L, Irhad S, Hodsoll J et al (2015) Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. Lancet 386:1835–1844
10. Westendorp W, Vermeij J, Zock E et al (2015) The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. Lancet 385:1519–1526
11. Schwarz S, Al-Shajlawi F, Sick C, Meairs S, Hennerici MG (2008) Effects of prophylactic antibiotic therapy with mezlocillin plus sulbactam on the incidence and height of fever after severe acute ischemic stroke: the Mannheim infection in stroke study (MISS). Stroke 39:1220–1227
12. Harms H, Prass K, Meisel C et al (2008) Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. PLoS One 3:e2158
13. Chamorro A, Horcajada JP, Obach V et al (2005) The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial. Stroke 36:1495–1500
14. Majkowski J, Kunicka J, Szabelska K, Cendrowski W (1982) Prophylactic use of penicillin G and ampicillin in stroke. I. Clinical observations. Neurol Neurochir Pol 16:261–267
15. Jauch EC, Saver JL, Adams HP Jr et al (2013) American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44:870–947
16. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470
18. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36:309–332
19. van de Beek D, Wijdicks EF, Vermeij FH et al (2009) Preventive antibiotics for infections in acute stroke: a systematic review and meta-analysis. Arch Neurol 66:1076–1081