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Overview

Management of acute ischemic stroke. The faster, the better

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Abbreviations:
AF – atrial fibrillation
CT – computed tomography
DVT – deep venous thrombosis
ED – emergency department
ER – emergency room
mRS – modified Rankin Scale
NIHSS – National Institutes of Health Stroke Scale
NNT – number needed to treat
PE – pulmonary embolism
rt-PA – recombinant tissue plasminogen activator
SICH – symptomatic intracranial hemorrhage
TIA – transient ischemic attack

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Abstract

Ischemic stroke is an emergency. Immediate ambulance transportation, cautious lowering of excessive blood pressures >220/120mmHg and abstention from heparin and aspirin are the most important measures in the preclinical setting. Hospital prenotification and clearly structured in-hospital pathways can help to reduce delay to treatment. Stroke patients are best treated in dedicated stroke units where vital parameters are monitored and stroke-related complications are recognized. Blood glucose should be in a normal range. Intravenous thrombolysis in the 3 hours window is the only approved efficacious, but time-dependent reperfusion therapy of acute ischemic stroke. Treatment with alteplase >3 to 4.5 hours from symptom onset and in elderly patients >80 years is beneficial and recommended by the European Stroke Organisation, but off-label. In severe stroke with CT-angiographical occlusion of a large intracranial artery, mechanical recanalisation is increasingly used. Only a small proportion of otherwise eligible stroke patients receive reperfusion therapy, mostly due to prehospital delay. The following article highlights on emergency management of acute ischemic stroke, and on strategies how the number of patients who benefit from acute stroke treatment and thrombolytic therapy may be increased.

INTRODUCTION

»Time is brain« is the slogan of acute ischemic stroke care, meaning that the earlier stroke treatment starts the better the outcome. Key of the concept is to minimalize the delay from symptom onset to therapy. Handling stroke as an emergency, comparable to acute coronary syndrome, is therefore most important in the preclinical and emergency room setting. Intravenous thrombolysis with alteplase within 3 hours is the only approved specific treatment of acute ischemic stroke. The benefit of thrombolytic therapy is time dependent *(1, 2)*. For every 10 minutes delay within 1-3 hours after stroke onset, 1 fewer patient out of 100 has a favourable outcome after systemic thrombolysis *(2)*.

In reality, the majority of ischemic stroke patients do not receive thrombolysis because they do not reach the hospital soon enough *(3, 4)*. For them, general acute stroke treatment including respiratory and cardiac care, fluid and metabolic management, blood pressure, glycaemic and temperature control, and treatment of stroke-related neurologic complications within the first hours to days after stroke is particularly important *(5)*. This article is focussed on the emergency management of acute ischemic stroke, and on strategies how delay to treatment may

be reduced. As a result, more patients would have access to acute stroke care, stroke units, and recanalization therapies.

Prehospital stroke management

Initialization of the emergency chain is the crucial first step for successful stroke treatment. However, time from symptom onset to alarming of emergency facilities accounts for the largest proportion of delay time in management of acute ischemic stroke *(6)*. Among the general population, there is discrepancy between good theoretical knowledge about stroke symptoms and taking action in the emergency situation *(7, 8)*: Frequently, family members rather than the patients themselves contact emergency services *(8)*. Informational campaigns distributed by mass media including TV, internet, social networks, and newspapers, must therefore encourage everybody to make an emergency call immediately, once stroke symptoms are suspected. Under the headline »Recognize & Respond«, for example, the »Power to end stroke« project of the American Stroke Association offers an internet based teaching of stroke signs followed by the instruction to call 911 (www.powertoendstroke.org).

Aside from raising public awareness towards stroke, training of emergency dispatchers, paramedics and emergency room staff improves preclinical stroke management. During emergency phone calls, stroke is often described as »collapse«, »fall«, »stroke« or »speech problems« *(9)*. Structured interviews with standardised questions can clarify the condition. Patients with facial droop, prior stroke or TIA *(7)* and severe clinical deficit *(10)* are most probable to receive a correct preclinical diagnosis of stroke, indicating that more subtle stroke symptoms may sometimes be misinterpreted or overseen. The Face-Arm--Speech Test (FAST) *(11, 12)* is a simple instrument that helps to identify stroke or TIA on scene or in the ER and assists further triage of patients.

Primary care doctors may also be involved in preclinical stroke management and should be encouraged that every suspected stroke needs urgent evaluation and emergency hospital admission *(13)*. Transportation by ambulance ensures faster arrival compared to private vehicles *(10,14)*. Whenever possible, transportation should be to the nearest hospital with a stroke unit. Prenotification of ED and stroke unit physicians during transport reduces in-hospital delay *(15, 16)* and leads to increased use of thrombolysis *(16, 17)*.

For transportation, patients should receive an intravenaus access and 0.9% saline by the ambulance staff. Aspirin and heparin are contraindicated before intracranial hemorrhage is excluded by CT scan. Hypertension should be tolerated up to 220/120 mmHg. Oxygen should be supplied if oxygen saturation falls below 95% *(18)*.

In-hospital management

Emergency room

Presentation to the emergency department via ambulance is in general the fastest way of referral for stroke patients *(10, 14, 19)*. In some cases (rural area, distance to hospital > 45 miles/72 km), helicopter transportation might be preferred *(20)*.

Immediate ER triage, neurological evaluation including NIHSS, general physical examination, laboratory tests, and a native CT scan (CT angiogram when large vessel occlusion is suspected) are needed *(18)*. Stroke and TIA mimics to be ruled out include epileptic seizures, syncopes, sepsis *(21)*, migraine with aura *(22)*, and hypoglycemia. Although not a part of routine implementation *(23)*, clearly structured in-hospital pathways can contribute to rapid evaluation and decision making in acute stroke. For example, by simultaneous alarming of all involved hospital staff, door to imaging time was significantly shortened in a recent single-center study *(24)*. After completion of diagnostic exams, stroke patients should be transported to the stroke unit, without delay.

Stroke Unit

Irrespective of age, gender, stroke subtype and severity, stroke unit care significantly reduces death, dependency and the need for institutional care in stroke survivors when compared to stroke patients treated in conventional wards *(25)*. Stroke units are dedicated wards with specialized multidisciplinary staff focussed on treatment of acute stroke and recognition of stroke related complications. Stroke teams consist of doctors, nurses, physiotherapists, occupational therapists, speech and language therapists and social workers *(26)* who collaborate in a coordinated way to do patient care. Personnel and technical equipment of a stroke unit should allow close assessment of the neurological status, monitoring of vital parameters within 72 hours after severe stroke, and provide early mobilization and sometimes rehabilitation *(18)*.

General stroke management

Whereas stroke is acutely life-treatening in the minority of cases, many patients need stabilization of vital functions during the first hours to days after ischemic stroke. Treatment strategies aim at normalizing respiratory and cardiac functions, glucose, blood pressure, and fluid balance, and at preventing stroke-related complications *(5, 18)*.

Cardiac monitoring

Stroke patients are at increased risk of cardiac arrhythmias, especially AF, myocardial infarction, heart failure and sudden death *(27, 28)*. Troponin levels are often slightly elevated during acute stroke, even in the absence of acute coronary syndrome, and thought to be due to stroke-related sympathoadrenal activation *(29)*. Therefore every stroke patient should have an ECG on admission. Further cardiac monitoring serves to maintain normal heart rates and can reveal paroxysmal AF as a common cause of stroke *(18)*. AF may also be detected by frequent pulse controls through trained nurses during the first 72 hours on the stroke unit, which is an evolving new concept due to the low sensitivity of Holter ECG at later time points.

Blood glucose

Hyperglycemia occurs frequently (30–40%; up to 60% in non-diabetics) in acute stroke and is associated with poor outcome and death, especially in patients without known diabetes *(30, 31)*. Hyperglycemia was shown to be associated with hemorrhagic transformation of stroke *(32)* and larger infarct volumes *(33, 34)*. However, it is uncertain if correction of elevated glucose levels improves clinical outcomes. To date, correction of glucose levels above 180 mg/dL (10 mmol/L) with insulin, and below 50mg/dl (2.8mmol/L) with 10–20% glucose or dextrose bolus is recommended *(18)*.

Blood pressure

As hyperglycemia, hypertension is common in acute ischemic stroke, and associated with increased risk of poor outcome *(35)*. Due to impaired cerebral autoregulation during acute stroke, every change in systemic blood pressure directly affects cerebral blood flow. Hypertension may result in hemorrhagic transformation of the infarcted area, whereas hypotension may cause further damage to the penumbra. Despite such pathophysiological considerations, the optimal blood pressure management in acute ischemic stroke is not known. It is also unclear whether early discontinuation from preexisting antihypertensive treatment (about 50% of patients) is necessary *(36)*. Beneficial effects of early hypertension control *(37)* could not be reproduced *(38)*. In the absence of conclusive data, current guidelines recommend moderate lowering of raised blood pressure over 220/ 120 mmHg, and over 185 mmHg systolic in thrombolysed patients using intravenous labetolol or urapidil *(18)*, approximately by 15–25% during the first 24 hours after stroke *(39)*. Sublingual nifedipine has been described to cause abrupt decrease in blood pressure *(40)*, and is therefore not a drug of first choice. In clinical practice, after permissive hypertension during the first 24 hours within the mentioned limits for nonthrombolysed and thrombolysed patients, antihypertensive medication may be continued or started from day 2.

Evidence how to handle hypotension is even more scarce. Low blood pressure at stroke onset is unusual *(41)*, and is recommended to be raised with saline 0.9% or volume expanders when associated with neurological deterioration. Inotropic support is only needed in patients with hypotension due to low cardiac output *(18)*.

Oxygen, fluid, and fever

Oxygen should be supplied (usually 2–4 L/min via nasal tube) if saturation is below 95%. Saline 0.9% is recommended for fluid replacement during the first 24 hours after stroke. Fluid balance and electrolytes should be further monitored in dysphagic patients with severe deficit or impaired consciousness. Pyrexia (body temperature >37.5°C) should be treated with paracetamol and prompt the search for infections *(18)*.

Infections

Bacterial pneumonia due to aspiration is one of the most frequent complications of acute ischemic stroke *(42)* and should be treated with antibiotics. Aspiration occurs in patients with dysphagia or impaired consciousness and may be prevented by feeding by nasogastric tube, pulmonary physical therapy, and early mobilization *(18)*. Prophylactic antibiotic treatment, in contrast, may be harmful *(43)*.

As pneumonia, urinary tract infections commonly occur in hospitalized patients, mostly due to indwelling catheters *(44)*. Roughly half the stroke patients expose incontinence at stroke onset *(45)*, so that urinary catheterization is at least temporarily needed. Antibiotics should be used once urinary tract infection is diagnosed. Bladder catheters should be removed as soon as possible. However, 25% and 15% of patients will be incontinent at discharge and one year after stroke, respectively *(45)*.

Deep venous thrombosis

Immobilization due to paresis is a risk factor for deep venous thrombosis (DVT) and consecutive pulmonary embolism (PE). Early mobilization, rehydration and subcutaneous low molecular weight heparin can reduce the risk of DVT and PE in stroke patients without increasing the risk of hemorrhage *(18, 46)*.

Falls

Many stroke symptoms – hemiparesis, ataxia, vertigo, visual field defect, lower limb hypaesthesia, cognitive impairment, and depression – as well as polypharmacy lead to impaired gait balance and expose patients to increased risk of injury and falls. Hypovitaminosis D can be seen within one week after hemiplegic stroke *(47)*. Falls occur in up to 25% of acute stroke patients, leading to serious injury, including hip fractures, in up to 5% *(48)*. Physical exercise *(49)*, mobilization, and supplementation of vitamin D *(50)*, calcium , and biphosphonates *(50, 51)* can reduce fracture rates among acute stroke patients and should be provided in the acute setting. Drugs leading to postural instability, e.g. neuroleptics, should be avoided whenever possible.

Agitation and delirium

Confusion, agitation and delirium are common problems in the acute phase of stroke. A search for underlying treatable causes often reveals dehydration, electrolyte dysbalance, fever, substance withdrawal, or nonconculsive epileptic seizures. When sedation or neuroleptics cannot be avoided, choice of drugs should take into account potential side effects. Sedation can lead to impaired consciousness and thus increase the risk of aspiration and falls, so substances with short half-time periods, such as lorazepame, may be preferred. Antipsychotics, among them risperidone *(52)*, have been associated with increased risk of cerebrovascular accidents in the elderly *(53)*, risk of myocardial infarction in demented patients on cholinesterase inhibitors *(54)*, and death *(52)*. The risk of cerebrovascular accidents seems to be greatest

within the first weeks of drug intake *(55)*, making the use of typical and atypical antipsychotics in the acute stroke setting even more hazardous. General recommendations are lacking, and prescription will be an individual decision based on comorbitidy and estimated harm if psychotic symptoms are left untreated. For example, a delirant stroke patient with Parkinson´s disease might be treated with quetiapine rather than risperidone or typical antipsychotics, whereas a demented stroke patient with aggression may benefit from low-dose risperidone or olanzapine .

Recanalization therapies

Intravenous thrombolysis

Systemic thrombolysis with rt-PA within 3 hours is the only approved evidence-based therapy of acute ischemic stroke *(56, 57)*. Beyond 3 to 4.5 hours, intravenous thrombolysis remains effective and safe *(1)*, but is yet unapproved by European medical authorities. Cerebral hemorrhage has to be excluded by CT scan before thrombolysis is started. As an off-label procedure, intravenous thrombolysis in the extended time window is routinely performed in experienced stroke centers. Data from the multicentre SITS-ISTR stroke registry showed that in 2009 there was a substantial increase (from 7% to 22%) in thrombolysis within 3 to 4.5 hours compared to 2008 *(58)*. However, the benefit of thrombolysis remains time-dependent (NNT in terms of a favourable outcome = 7 within 3 hours, 14 by 3 to 4.5 hours) *(1)*. Overall, the risk of SICH and mortality are slightly higher in patients thrombolysed within the extended time window, but the proportion of patients with favourable clinical outcome after 90 days is similar *(58, 59)*.

Thrombolysis >80 years of age

About 30% of strokes occur in people >80 years of age *(60, 61)*. Whereas approval criteria restrict thrombolysis to younger patients, it is now clear that older age is not a reason to preclude someone from treatment: Risk and benefit must be weighted. Elderly stroke patients have higher bleeding rates. Mortality is also higher, but so is pre-stroke comorbidity. However, functional outcome in terms of mRS is significantly better in patients >80 years after thrombolysis vs. without, and similar to younger patients *(62, 63)*.

Mechanical recanalization

In recent years, an increasing number of mechanical recanalization devices have been used to treat severe strokes with intracranial large artery occlusion as shown by CT angiography. The rates of good outcome (mRS = 0–2) in creased to 45 % with the latest techniques (Table 1) – rather acceptable for patients having very severe strokes *(64–67)*. For selection of patients the mismatch of cerebral blood flow and cerebral blood volume on contrast enhanced CT is used more and more instead of the time window (Figure 1). Perfusion CT has the advantage of being fast, widely available and less affected by artefacts than diffusion weighted and perfusion weighted magnetic resonance imaging.

Mobile Stroke Unit

Maximal benefit from thrombolysis would be obtained if started immediately after symptom onset. A new approach to minimize the delay-to-treatment-decision is the concept of mobile stroke units. These are high-tech ambulance cars equipped with a CT scanner, teleradiological connection, and laboratory. The aim is to start in-

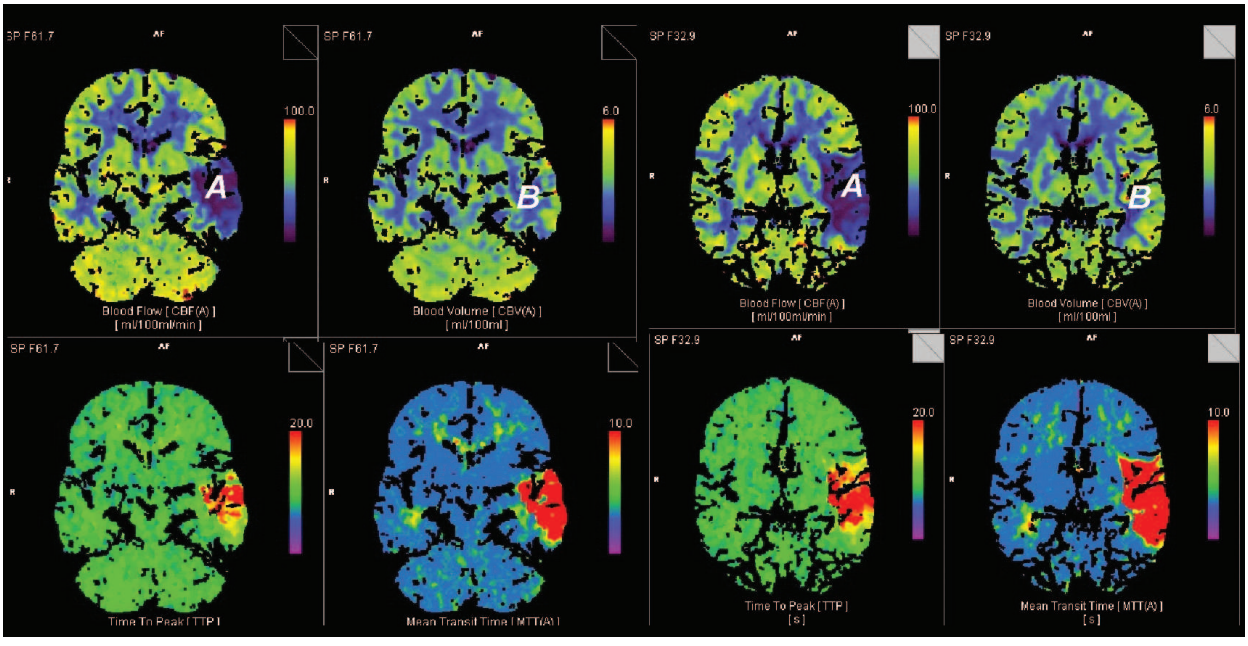

Figure 1. *Contrast enhanced perfusion CT allows to differentiate regions with reduced cerebral blood flow (A) and normal cerebral blood volume (B). This mismatch permits mechanical recanalization efforts.*

TABLE 1

Mechanical recanalization devices in comparison to the results of NINDS and SITS-MOST.

	NINDS rt-PA	SITS-MOST	PROACT II	Multi-MERCI	Penumbra Pivotal	Solitaire (Pilot)
Number of patients	312	6483	121	164	125	20
NIHSS	18	12	17	19	18	19
Recanalization (%)	–	–	66	57	82	90
90 d-mRS 0–2 (%)	28	54	40	36	25	45

travenous thrombolysis during transportation, once eligibility criteria have been checked. Two pilot projects are currently ongoing in Germany. One of them reports a dramatic reduction in alarm-to-needle times (time from emergency call to beginning of thrombolysis) when patients are transported by, and treated in the mobile stroke unit *(68)*.

CONCLUSION

Every minute counts in the treatment of acute ischemic stroke. Raised stroke awareness within the population, rapid diagnosis by paramedics and primary care doctors, transportation by ambulance cars, hospital prenotification and well organized in-hospital pathways contribute to early beginning of stroke therapy. The extended time window for systemic thrombolysis and recent data supporting thrombolysis in elderly patients >80 years of age offer the possibility that more patients receive this specific therapy for acute ischemic stroke. Acute general stroke management is best done at a multiprofessional stroke unit for 48–72 hours and deals with stroke-related metabolic, cardiorespiratory, inflammatory, and neuropsychiatric problems.

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