Management of Acute Ischemic Stroke

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10.1 Introduction

Cerebral stroke is the second leading cause of death and the third cause of permanent disability worldwide. The incidence and prevalence rates of cerebral stroke increase with increasing age; in Italy, an overall prevalence of 6.5% and an incidence between 144 and 293 cases/100,000 inhabitants/year are estimated for the population over 45 years of age.

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The impact of stroke on public health systems is massive, with an estimated annual expenditure in Italy of around €16 billion for about 100,000 hospitalizations (data from Osservatorio Ictus Italia 2018).

Ischemic stroke is the most common subtype of this disease, causing 80% of all stroke cases. About 15% of the remaining cases are intraparenchymal hemorrhages, less than 5% are subarachnoid hemorrhages, and less than 2% cerebral venous thrombosis.

In the last two decades, the progress in therapeutic interventions for ischemic stroke has dramatically changed the outcome of patients affected by this pathology. Therapies aimed at reperfusion of occluded cerebral vessels are increasingly implemented worldwide and accepted as the standard of care for acute ischemic stroke. Consequently, management strategies for these patients have adapted to the complexity and potential complications of these treatments. In this chapter are reviewed the clinical characteristics of ischemic stroke and the main clinical challenges that can occur during the acute phase of ischemic stroke.

10.2 Ischemic Cerebral Stroke

Ischemic stroke is defined as a focal neurological deficit lasting for more than 24 h, caused by the occlusion of one or more branches of the cerebral arteries. The cause of occlusion can be traced to various pathogenetic mechanisms, among which the most frequent are cardiac embolism, arterio-arterial embolism, and in-situ atheromatous or dissecative pathology of cerebral vessels [1].

A transient ischemic attack (TIA) is defined instead as a focal neurological dysfunction lasting less than 24 h without evidence of cerebral infarction on brain imaging.

The main risk factors for stroke are atrial fibrillation, age, hypercholesterolemia, carotid atheromasia, smoking, diabetes mellitus, and excessive alcohol consumption [2–5]. Furthermore, modifiable and environmental conditions such as a sedentary lifestyle, obesity, OSA syndrome, air pollution, and excessive psychosocial stress seem to represent additional risk factors [6].

10.2.1 Clinical Features

The symptomatology of stroke is related to the location and extent of the ischemic lesion. Very frequent symptoms of stroke are characterized by the sudden onset of the following: unilateral hyposthenia with variable intensity (hemiparesis and hemiplegia), unilateral sensory deficit (hemihypoesthesia), unilateral campimetric deficit (hemianopsia), and difficulty in articulation of language (dysarthria) or in the production/understanding of language (motor or sensory aphasia).

It is important to consider that, due to the complex anatomy of the central nervous system, a stroke can manifest through a vast combination of clinical signs.

Less frequent symptoms of a stroke are isolated vertigo, movement disorders (hemiballism), amnesia, and isolated cranial nerve deficits.

Focal symptoms may also appear associated with signs of general dysfunction of the central nervous system such as seizures, alterations of consciousness, and impairment of the respiratory function.

10.2.2 Initial Management, Clinical Assessment, and Monitoring of the Acute Stroke Patient

The objectives of the initial approach to the stroke patient include a general clinical framework with particular attention to the stability of vital functions and to the evaluation of the patient's eligibility to undergo pharmacological fibrinolysis and/or endovascular thrombectomy.

An accurate but fast collection of medical history is essential for the exclusion of any conditions that may contraindicate reperfusion therapies. Particular attention must be paid to anticoagulant therapies (TAO, DOACs, and LMWH). Detailed information regarding any preexisting and chronic pathological conditions may aid the clinician in identifying the cause of ischemic stroke, but if not immediately available, they should not delay the beginning of reperfusion therapy.

It is crucial to establish the time of onset of stroke symptoms. For patients who are unable to report this information, the time at which the patient was seen well by family members or caregivers will be considered as the onset of symptoms.

A neurological examination is necessary for the assessment of the severity of the stroke and the evaluation of the patient's eligibility for reperfusion treatments. The use of standardized assessment scales facilitates both the identification of patients with a possible stroke in the prehospital phase (Face Arm and Speech Test) and changes in stroke severity during hospital management (National Institute of Health Stroke Scale).

10.2.3 Assessment of Vital Functions

An evaluation of the basic vital functions aimed at ensuring the stability of respiration and circulation (Airway Breathing Circulation) is fundamental in the approach to all patients with ischemic stroke, similarly to patients with other acute conditions with potentially severe and rapid evolution. Patients with a stroke of the brainstem or with large cortical strokes may experience an altered state of consciousness that impairs respiratory function or the ability to protect the airways, with the need for endotracheal intubation.

The initial management of the patient with acute ischemic stroke involves a series of diagnostic investigations aimed at assessing eligibility for reperfusion therapies. Given the time-dependency of these therapies, the clinical evaluation of stroke patients should be completed as quickly as possible. In this complex diagnostic-therapeutic phase, the clinician may find useful to use procedural protocols and flow charts in

order to reduce the chances of diagnostic errors or of performing unnecessary diagnostic tests; one of the most used series of protocols for the management of the patient with acute neurological pathology is The Emergency Neurological Life Support, an initiative of the Neurocritical Care Society [7].

10.2.4 Basic Diagnostic Tests

All patients with suspected ischemic strokes should undergo diagnostic investigations that are absolutely necessary for assessing the feasibility of reperfusion treatments, primarily pharmacological fibrinolysis.

These tests are:
- Basal-cerebral CT or brain MRI
- Blood glucose dosage
- SpO_2 monitoring
- Arterial blood pressure monitoring

Other investigations recommended in the immediate hospital phase are:
- ECG
- Cardiac enzymes dosage
- Complete blood count
- Coagulation profile

Waiting for the result of the latter should not delay the beginning of fibrinolytic therapy if the patient is eligible after the initial assessment.

For selected patients, further investigations may be necessary to rule out conditions that may mimic an ischemic stroke or increase the risk of bleeding during the fibrinolysis procedure [8–10]. In order to help a differential diagnosis, the following tests can be requested:

- Dosage of serum electrolytes
- Tests of liver function
- Toxicological screening
- Blood alcohol level
- Pregnancy test
- Blood gas analysis
- Chest X-ray
- Lumbar puncture
- EEG

10.2.5 Airway Control

In order to limit neurological damage due to lack of oxygen, hypoxemia should be avoided. Peripheral O_2 saturation should be monitored for at least 48 h after hospital admission for acute stroke. International guidelines recommend a SpO_2 higher than

94% for patients with acute ischemic stroke. Appropriate interventions (nasal cannulas, noninvasive ventilatory support, and mechanical ventilation) must be considered in case of reduced respiratory function with hypoxemia. The need for mechanical ventilation is more often associated with subtentorial strokes or with hemispheric strokes involving more than two-thirds of the middle cerebral artery territory [11]. The decision regarding intubation of the ischemic stroke patient is however based on the clinical condition; no definitive indications based on blood gas or neuroimaging parameters alone are currently available.

10.2.6 Management of Changes in Body Temperature

About a third of patients with acute ischemic stroke present hyperthermia. Hyperthermia during ischemic stroke is associated with an unfavorable outcome. This is believed to be due to the fact that hyperthermia causes a general increase in the metabolic demands of the brain parenchyma (due to a higher cerebral metabolic rate of oxygen). Furthermore, it has been hypothesized that ischemia of cerebral parenchyma causes the formation of free radicals and the release of excitatory neurotransmitters, such as glutamate and dopamine; these processes seem to be amplified by the increase in body temperature [12–14].

The management of hyperthermia should focus on the identification of possible causes of infection and on control of body temperature through the use of antipyretic drugs.

10.2.7 Cardiovascular Monitoring and Blood Pressure Management

Cardiac rhythm monitoring is recommended in the first 24–48 h after admission of acute stroke patients. Such monitoring, in some patients, allows for the recognition of emboligenic cardiac arrhythmia as a possible cause of stroke and contributes to the exclusion of cardiac problems that can occur as a consequence of the stroke itself.

Most patients with acute ischemic stroke have high blood pressure values in the first hours after symptom onset; these alterations are believed to be due in part to an increase in catecholamine release due to sympathetic overactivity [15]. This could represent a defense mechanism aimed at increasing perfusion at the level of ischemic areas [16] where the mechanisms of brain auto-regulation of blood flow would not be effective [16, 17].

Several observational studies have shown a worse outcome in patients who undergo a pharmacological reduction of the systolic blood pressure greater than 20 mmHg within the first 24 h after the onset of symptoms [18], even though subsequent meta-analyses of randomized trials did not confirm these results [19, 20].

To date, international guidelines recommend abstaining from the treatment of acute hypertension in patients with ischemic stroke who are not candidates for fibrinolytic treatment unless the values exceed 220/120 mmHg, or in the case of concurrent acute conditions such as acute myocardial infarction, eclampsia, hypertensive encephalopathy, and aortic dissection [8, 21].

In the case of patients who undergo pharmacological fibrinolysis, due to the increased risk of intraparenchymal cerebral bleeding, the value above which antihypertensive treatment should start is 180/110 mmHg [8].

If a reduction in blood pressure is necessary, Guidelines recommend the use of Labetalol, Nicardipine, or Clevipidine as first choice therapies [8].

10.2.8 Neuroimaging in the Acute Phase of Stroke

A noncontrast cerebral CT scan is sufficient for the beginning of fibrinolytic therapy as it allows the exclusion of intracranial hemorrhages, an absolute contraindication to pharmacological fibrinolysis. This exam also allows the detection of early signs of cerebral infarction that can be quantified using the Alberta Stroke Program Early CT Score (ASPECTS); a standardized approach that divides the vascular territory of the middle cerebral artery into 10 areas; using this scoring system one point will be subtracted for each area interested by ischemic hypodensity. Low ASPECTS scores predict an unfavorable outcome along with an increased risk of bleeding following thrombolytic therapy.

However, a brain CT does not provide direct information on the possible site of vascular occlusion. In order to identify the site of vascular occlusion, vascular neuroimaging techniques such as CT or MRI angiography can be used.

Single-phase CT angiography requires the use of contrast media, a greater experience in interpreting the result, and longer execution times than basal brain CT; nevertheless, this examination allows an accurate evaluation of the cerebral arterial circulation making it possible to identify occlusions of the main branches of the intracranial arterial vessels. The use of the multiphase technique also allows a more precise evaluation of the leptomeningeal collateral circulation as well as a more accurate visualization of occlusions of distal small caliber vessels.

Based on these advantages, CT angiography is the most used technique to evaluate the indication for endovascular reperfusion strategies. Extending the exam to the aortic arch and epiaortic vessels can also provide useful information for the planning of the endovascular procedure.

In recent years, increasing attention has been drawn to perfusion brain imaging techniques; in particular, CTP (CT Perfusion), MRP (MRI Perfusion), and MR techniques based on the evaluation of mismatch between specific sequences (MRI-DWI and FLAIR). The use of these resources is particularly useful in cases where no information is available regarding the time of onset of symptomatology; in these situations, the evaluation of the ischemic penumbra (the portion of ischemic brain tissue that has not yet undergone necrosis) is crucial. CTP allows the assessment of cerebral hemodynamics through the quantification of:

- Mean transit time (MTT), consisting of the difference between arterial transit time and venous efflux.
- Cerebral blood flow (CBF), consisting in the volume of blood passing through a given amount of brain tissue per unit of time.
- Cerebral blood volume (CBV), defined as the volume of blood in a given amount of brain tissue.

Through the analysis of these parameters, it is possible to differentiate between areas of irreversible ischemic necrosis (characterized by an increased MTT and reduced CBF and CBV), and areas of ischemic penumbra (in which the CBV will be preserved or even increased, thanks to the blood supply from collateral circulation).

Through the use of perfusion neuroimaging and MRI-DWI techniques, it has recently been demonstrated that patients with symptom onset up to 24 h before the beginning of endovascular thrombectomy might benefit from this treatment if the presence of a mismatch between the area of ischemic necrosis and the area of penumbra is shown [9, 10].

10.2.9 Treatment Strategies in Acute Ischemic Stroke

The treatment of acute ischemic stroke consists of procedures aimed at restoring blood flow to the area of the cerebral parenchyma affected by ischemia. To date, two types of therapeutic strategies are available for this purpose: pharmacological fibrinolysis and endovascular thrombectomy. The two approaches can be implemented individually or in combination depending on different factors among which the most important are the location of the arterial occlusion and the time interval between the onset of symptoms and the arrival in the hospital. Both treatments are time-dependent as they aim at the reperfusion of the "ischemic penumbra", that is the part of hypoperfused brain tissue that surrounds the "ischemic core" and that, unlike the latter, has not yet undergone tissue necrosis. In the event of a large vessel occlusion (LVO), pharmacological fibrinolysis is useful in around 30% of patients. Recently, a series of clinical trials have demonstrated the efficacy of endovascular treatment (EVT) in the treatment of patients with LVO, particularly when this technique is performed in combination with pharmacological fibrinolysis.

10.3 Intravenous Thrombolysis

In the 1990s, the Food and Drug Administration (FDA) approved the use of recombinant tissue plasminogen activator (rTPA) as a therapy for acute ischemic stroke, administered within 3 h of symptom onset. This was based on the results of one randomized controlled trial (National Institute of Neurological Disorders and Stroke, NINDS), which demonstrated improved outcomes in terms of functional independence in patients treated with rTPA compared to placebo [22]. Subsequently, a second RCT (European Cooperative Acute Stroke Study III, ESASS 3) confirmed the benefit of this therapeutic approach also in patients treated up to 4.5 h after the onset of symptoms [23]. Both studies showed an increased risk of symptomatic cerebral hemorrhage in patients treated with fibrinolytic, but the benefit of therapy exceeded this risk (Table 10.1).

Table 10.1 Summary of the results of the NINDS and ECASS-3 studies

	iv rTPA	Placebo	*p* value
NINDS			
Number of patients	312	312	
Mean NIHSS at onset	14	15	
Favorable outcome at 3 months (mRS 0–1) *N* (%)	133 (42.6)	83 (26.6)	<0.01
Symptomatic intracranial hemorrhage	20 (6.4)	2 (0.6)	<0.01
ECASS 3			
Number of patients	418	403	
Mean NIHSS at onset	9	10	
Favorable outcome at 3 months (mRS 0–1) *N* (%)	219 (52.4)	182 (45.2)	0.04
Symptomatic intracranial hemorrhage	33 (7.9)	14 (3.5)	<0.01

iv-rTPA recombinant tissue plasminogen activator, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale

10.4 Endovascular Treatment

Between 1999 and 2010, the efficacy of endovascular treatments was investigated in four randomized controlled trials. These studies have tested the effects of intraarterial administration of fibrinolytic (streptokinase, urokinase, and rTPA) eventually associated with the use of different devices for mechanical thrombectomy. None of the studies showed a significant advantage of these techniques compared to pharmacological fibrinolysis [24–27].

Between 2010 and 2015, several studies based mainly on the use of devices for the mechanical removal of emboli (stent retrievers) have provided the first encouraging results concerning the techniques of endovascular thrombectomy.

The study "Multicenter Randomized Trial for Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN)" first showed a tendentially better outcome and the absence of a significant difference in terms of morbidity and adverse events in the group of patients treated with EVT [28]. The studies "ESCAPE", "SWIFT PRIME", and "REVASCAT" provided preliminary results that confirmed those of MR CLEAN.

In 2015, based on the results provided by these trials, the main international guidelines (American Heart Association/American Stroke Association) supported the use of EVT for the treatment of patients with ischemic stroke due to proximal occlusion of anterior cerebral circle vessels (distal tract of the internal carotid and proximal tract of the middle cerebral artery) within 6 h of symptom onset, in association with pharmacological fibrinolysis [29].

Recently, the DAWN study showed that EVT is effective in patients with ischemic stroke due to the occlusion of a large vessel of the anterior cerebral circulation up to 24 h from symptom onset if there is evidence of a mismatch between the neurological deficit and the area of ischemic necrosis. In this trial, the patients underwent a rigid selection protocol based on the results of the perfusion CT study for the evaluation of the ischemic core and the ischemic penumbra [30]. The results of the DAWN trial seem to encourage a shift of the "time is brain" paradigm toward

Table 10.2 Summary of the results of the main RCTs that have investigated the efficacy of endovascular therapy

	Number of patients Tot/EVT	Time window	Imaging criteria	General anesthesia	rTPA pre EVT	Favorable outcome[a]
MR CLEAN NEJM 2015	500/223	0–6 h	no	38%	87%	33% vs. 18%
ESCAPE NEJM 2015	215/165	0–12 h	ASPECTs (CT)	9%	73%	53% vs. 29%
SWIFT-PRIME NEJM 2015	196/98	0–6 h	ASPECTs/ CTP/MRP	37%	98%	60% vs. 35%
REVASCAT NEJM 2015	206/103	0–8 h	ASPECTs (CT/MR)	7%	78%	44% vs. 28%
EXTEND-IA NEJM 2015	70/35	0–6 h	CTP/MRP	36%	100%	71%
DAWN NEJM 2018	206/107	6–24 h	CTP/MRP	10%	5%	49% vs. 13%
THRACE Lancet 2016	414/204	0–5 h	No	32%	100%	53% vs. 42%

rTPA recombinant tissue plasminogen activator, *EVT* endovascular treatment, *CTP* CT perfusion, *MRP* MR perfusion, *ASPECTs* Alberta Stroke Program Early CT Score
[a]Favorable outcome: modified Rankin Scale (mRSC) <2 to 90 days

a therapeutic approach guided by the quantification of brain tissue that can benefit from the restoration of blood circulation for patients with symptom onset between 6 and 24 h prior to access to care (Table 10.2).

The most recent guidelines (AHA/ASA 2018) suggest that perfusion neuroimaging should not delay the administration of rTPA or EVT in patients eligible for these therapies, but in selected patients, such investigations may provide important information for the mechanical thrombectomy between 6 and 24 h after the onset of symptoms [8].

10.5 Choice of the Therapeutic Strategy

With regard to pharmacological fibrinolysis using Alteplase, the time window in which the drug has a good chance of improving the outcome of the stroke patient is 4.5 h from the onset of symptoms.

Similarly, the success of mechanical thrombectomy is dependent on the time between the onset of symptoms and the beginning of the treatment. The time

window for the implementation of this therapeutic strategy can be much wider than that for pharmacological fibrinolysis, depending on the results of advanced neuroimaging investigations.

The general indications for the choice of reperfusion treatment, or for the combination of the available strategies, can be summarized in relation to the time passed from the onset of symptoms:

- **Possibility of starting treatments within 4.5 h of symptom onset**
  The initiation of fibrinolytic therapy with Alteplase is indicated as soon as possible after ascertaining the patient's eligibility. At the same time, the patient should also be evaluated for endovascular thrombectomy.
  The latest international guidelines recommend that the eligibility for fibrinolytic treatment and for endovascular treatment should be assessed simultaneously [31].
- **Time interval 4.5–6 h from the onset of symptoms**
  After 4.5 h from the onset of symptoms, the use of Alteplase is not recommended. Patients in this time window should be evaluated for endovascular thrombectomy.
- **Time interval 6–24 h from symptom onset**
  Patients in this time window should be evaluated for the appropriate endovascular procedure at specialized centers based on the results of advanced neuroimaging investigations (AngioTC, perfusional CT, and NMR-DWI).
- **Onset of symptoms not known/onset upon awakening**
  For patients who are unable to report the time of symptoms onset, this must be considered as the moment in which the patient was seen in normal conditions by a family member or acquaintance, as this allows for the categorization of the patient in one of the time intervals described above. Patients with symptoms onset upon awakening can be evaluated for fibrinolytic or endovascular procedures based on the results of perfusional neuroimaging investigations.

10.6 Complications and Potential Critical Events in the Setting of Reperfusion Therapies

Reperfusion therapies require a strong and mindful integration of the efforts of several specialists and emergency personnel in a multidisciplinary team. Anesthesiologists and intensivists are progressively more involved in acute stroke care due to the constant increase in the number of patients treated with intravenous thrombolysis and endovascular treatments and to the consequent increase of critical events and need for anesthesiological assistance associated with these treatments.

Here are reviewed some of the potential clinical challenges for the anesthesiologist during these procedures.

10.7 Potential Critical Events During Intravenous Thrombolysis

The majority of patients treated with rTPA do not require critical care resources; nevertheless, eventual complications of fibrinolytic treatments can be severe and may require urgent critical care. Patients who receive intravenous thrombolysis for

acute ischemic stroke should undergo frequent checks of vital signs and neurological status, in order to allow early detection of complications.

Potential critical events and side effects of fibrinolytic therapy are discussed below.

10.7.1 Brain Hemorrhage

Treatment with Alteplase is associated with an increased risk of cerebral hemorrhage in the early stages of ischemic stroke. This complication may occur during treatment or in the following hours through a deterioration of the neurological conditions associated with symptoms such as headache, nausea, or sudden changes in vital parameters. Anticipating high-risk patients is important; risk factors for the development of intracerebral hemorrhage after stroke are a large infarct volume (>1/3 of the middle cerebral artery territory), frank ischemic hypodensity on CT scan within 6 h of symptoms onset, and large vessel occlusion.

If during thrombolysis symptoms suggestive of cerebral hemorrhage occur, the treatment must be suspended and the patient must undergo an urgent brain CT scan. If hemorrhage is confirmed on imaging, therapies aimed at slowing the extent of the bleeding should be considered.

There is no specific treatment for this type of bleeding and the effectiveness of available treatments has not been proven. Treatment options include: aminocaproic acid and tranexamic acid, cryoprecipitate, prothrombin complex, fresh frozen plasma, vitamin K in the case of patients treated with warfarin before the administration of Alteplase, and platelet concentrates in the case of patients with thrombocytopenia. Systolic blood pressure (SBP) may be managed in accordance with existing brain hemorrhage guidelines (SBP <140 mmHg).

It is also advisable to request a neurosurgical evaluation to assess the eventual indication for surgical evacuation of the hematoma despite the fact that the efficacy of this procedure, in this particular condition, has not been proven by randomized controlled studies [32].

10.7.2 Systemic Hemorrhage

Mild peripheral bleedings, including bleeding at the level of venous catheters, gingival bleeding, petechiae, and hematomas in the limbs and trunk are common complications of Alteplase therapy. Usually, the extent of these bleedings does not require the suspension of fibrinolytic treatment.

Rarely severe hemorrhages may occur; of these, the most feared is hemopericardium, which may arise during treatment with Alteplase in patients with recent extended myocardial infarction [33]. The predominant symptom of hemopericardium is a sudden reduction in blood pressure. In this case, an urgent echocardiographic examination is advisable to exclude cardiac tamponade.

If the clinical suspicion of major bleeding (gastrointestinal tract, heart, and genitourinary tract) arise, it is appropriate to interrupt the administration of fibrinolytic therapy and carry out the appropriate urgent diagnostic tests.

10.7.3 Angioedema

This is a relatively frequent complication with an estimated incidence of 2–8% of patients receiving treatment with Alteplase [34, 35]. Patients treated with ACE inhibitors and patients with stroke located in the insular and frontal cortex seem to have a higher risk of developing angioedema [36, 37].

In most cases, this condition occurs at the side of the tongue, more often ipsilaterally to the ischemic lesion, and does not require orotracheal intubation. More rarely, angioedema can cause airway obstruction, especially when it involves the uvula, the soft palate, or the larynx. In these cases, it is necessary to evaluate the interruption of treatment with Alteplase and evaluate the possible need for orotracheal intubation.

The specific management of severe angioedema includes the maintenance of airway patency, which could be more difficult due to the modification of the normal airway anatomy, and the administration of corticosteroids, antihistaminics, and possibly complement inhibitors [8].

10.8 Potential Critical Events During Endovascular Treatment

Endovascular recanalization is a complex urgent procedure that requires optimal management of all the organizational and clinical problematics that may arise during the acute phase of ischemic stroke and involves preinterventional preparation of the patient, interventional monitoring, eventual analgesia and sedation, and management of complications.

The most important problematics of potential critical care interest are discussed below.

10.8.1 Interhospital Transfers, "Drip and Ship"

The term "drip and ship" refers to the quick administration of rTPA to a stroke patient in a primary medical center, followed by the urgent transfer toward a more advanced medical facility where EVT can be performed.

Drip and ship is an increasingly frequent phase in the early management of patients with ischemic stroke due to the discrepancy between the number of centers that can offer intravenous fibrinolysis (Spoke centers) and the number of highly specialized centers in which EVT is performed (Hub centers). With the progressive extension of indications and time window for EVT, the number of patients considered eligible for this procedure is constantly increasing. This implies an increase in the number of urgent interhospital transports from Spoke to Hub centers. This type of interhospital transport represents a crucial phase for therapeutic success as it allows access to an effective and safe treatment in a short time; however, the complexity of the patients' conditions and the simultaneous use of the fibrinolytic expose the patients who undergo this type of transfer to a greater risk of adverse

events. A study that assessed the safety of "drip and ship" on 44,667 patients found that patients who undergo drip and ship had a higher chance of developing intracerebral hemorrhage (OR 1.41; 95% CI 1.25–1.58) and a higher in-hospital mortality rate (OR 1.46; 95% CI 1.22–1.46) [38].

10.8.2 Blood Pressure Management

To date, an optimal blood pressure target is not available for patients who are undergoing EVT. Guidelines suggest the maintenance of a systolic pressure value between 150 and 180 mmHg before and during the procedure, and below 140 mmHg once the recanalization of the occluded vessel is obtained [8]. Systolic values below 150 mmHg are not recommended during the procedure as it is believed that lower values can impair cerebral collateral circulation that occurs during the occlusion of large arterial branches [8, 39]. Several studies have shown that even modest lowering of MAP during EVT might be associated with a worse outcome [40–42].

10.8.3 Choice of Sedation

Procedural sedation during mechanical thrombectomy can be obtained with conscious sedation or with general anesthesia depending on several factors, among which the most important are the patient's state of consciousness and hemodynamic conditions, as well as preferences and experience of the center where the procedure is carried out (Table 10.3).

Table 10.3 Comparison of indications, potential advantages, and disadvantages of the type of sedation chosen for the endovascular procedure

General anesthesia	Conscious sedation
Main indications	
• Severe neurological impairment or agitation	• Collaborating patient able to maintain supine position without pain
• Hemodynamic instability	• Hemodynamic stability
• Loss of airway protection capacity	• Preserved airway protection capacity
Potential advantages	
• Immobility of the patient during the procedure	• Less risk of post-procedural respiratory complications
• Better image quality	• Possibility of evaluating the neurological status during the procedure
• Better operator comfort	• Less risk of hypotension
• Better control of respiratory parameters ($PaCO_2$)	• Minimum delay in the start of the procedure
Potential disadvantages	
• Delay in the beginning of the procedure	• Risk of perforation or dissection caused by movement
• Risk of hypotension	• Lower image quality
• Inability to assess changes in neurological status during the procedure	• Possible need for conversion in general anesthesia

To date, the impact of the choice of sedation on the outcome of the procedure is still not completely clear. A systematic review and meta-analysis conducted on six studies (including three RCTs), in which second-generation devices for EVT were used, did not find significant differences in the outcome of patients undergoing conscious sedation compared with patients undergoing general anesthesia [43].

Recently, a single-center trial (GOLIATH) [44] demonstrated a more favorable clinical outcome in the group of patients treated under general anesthesia compared to those who underwent conscious sedation (OR 1.91, 95% CI 1.033); this trial considered the modified Rankin Scale score 3 months after the procedure and the improvement in neurological deficit 24 h after the procedure.

However, the potentially unfavorable effects of general anesthesia should be considered in patients with acute ischemic stroke; in particular, the repercussions of general anesthesia on arterial pressure and the delay in the beginning of the intervention due to sedation and orotracheal intubation procedures. The same study found tendentially lower values of mean arterial pressure (MAP) in patients treated under general anesthesia, as well as a slight increase in the delay of EVT in this group of patients.

In some cases, it may be necessary to switch from conscious sedation to general anesthesia during a procedure. This can happen due to various reasons such as technical difficulties, agitation of the patient, and onset of complications.

10.8.4 Extubation

Patients who at the end of EVT under general anesthesia are hemodynamically stable and meet the clinical criteria for extubation (e.g., the ability to protect the airways, maintaining an adequate level of consciousness and absence of intraprocedural complications) can be extubated in the angiography room and transferred to the stroke unit. Extubation should be performed as soon as safely possible in order to minimize the risks associated with prolonged mechanical ventilation (e.g., ventilation-associated pneumonia). The conditions that most often make extubation unsafe are represented by respiratory comorbidities and the extension of cerebral infarction. The decision to extubate patients with severe ischemic stroke is made even more difficult by the fact that the clinical criteria for extubation are often less reliable by impaired brain function [45, 46].

10.8.5 Complications of Endovascular Treatment

Unlike fibrinolytic treatment, EVT is not associated with an increased risk of cerebral hemorrhage [47].

In the major clinical trials, a low incidence of adverse events due to the endovascular procedure was observed: these include the appearance of ischemic lesions in arterial territories other than the initial one [48], the formation of peripheral hematomas and pseudoaneurysms at the level of sites of vascular access, and arterial

dissections or perforation caused by catheters [39, 49–51]. Another complication is arterial vasospasm; this condition is often self-limiting, but sometimes requires treatment with an in-situ infusion of vasodilators (nimodipine).

10.9 Intensive-Care Management of Acute Stroke Patients

At the end of the reperfusion procedures, hemodynamically stable patients can be transferred to the Stroke Unit for continued monitoring and care. However, some patients may need admission to an intensive care unit (ICU) after the acute phase due to stroke severity or treatment complications. The conditions that most often necessitate transfer to intensive care are represented by reduction of airway protection reflexes, hemodynamic instability, sudden reduction of the state of consciousness, and signs of extensive cerebral edema.

Some aspects of the ICU management of the ischemic stroke patient are of particular importance, as discussed below (Fig. 10.1).

10.9.1 Cerebral Edema

Patients with large strokes may experience a deterioration of the neurological conditions due to the mass effect of ischemic brain tissue on adjacent structures, caused by the cytotoxic edema that develops in the context of the ischemic lesion.

The treatment of cerebral edema can be pursued through the use of anti-edema drugs or through decompressive craniectomy in more severe cases.

The use of mannitol, hypertonic saline, or the induction of moderate hypocapnia (PCO_2 target 32–34 mmHg) is considered reasonable in order to reduce cerebral edema [8].

10.9.2 Decompressive Craniectomy

Decompressive craniectomy is a life-saving procedure that allows the reduction of the mass effect on the structures of the brainstem by the edema of large hemispherical strokes. Several studies have investigated the consequences of craniectomy. The results of these studies suggest that patients less than 60 years of age suffering from hemispheric stroke with severe neurological deterioration due to mass effect within 48 h of the ischemic event can benefit from this procedure. The analysis of the results of randomized trials found a reduction in mortality and degree of functional dependence at 12 months from stroke in patients undergoing craniectomy compared to patients treated with medical therapy alone. For patients over the age of 60, the benefit of the procedure is less marked, both in terms of reduction of mortality and improvement of functional recovery over time. According to the most recent international recommendations, it is reasonable to perform decompressive craniectomy in patients <60 years with severe cerebral edema (COR IIa, LOE A) and it is possible to evaluate the indication for this procedure also for patients aged >60 years [8].

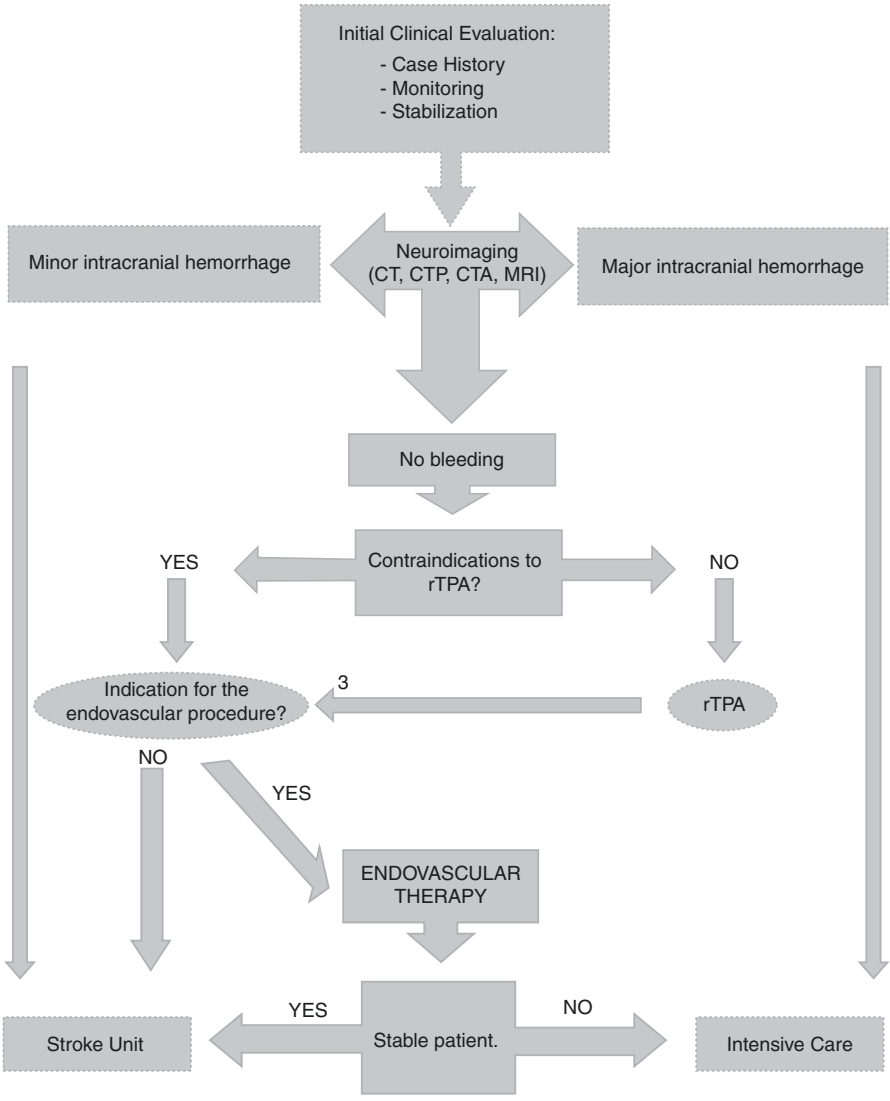

Fig. 10.1 Flow chart for the management of patients with acute ischemic stroke. (1) All patients who have an acute neurological deficit compatible with stroke should undergo the initial evaluation for ischemic stroke. (2) Minor vs. major intracranial hemorrhage: no criteria are available for the definition of intracranial bleeding as major or minor. The interpretation of the condition must be based on the evaluation of different clinical and neuroimaging parameters, for example: site and size of bleeding (subarachnoid, subdural, or intraparenchymal), stability of vital signs, treatment with anticoagulants, etiology of bleeding (spontaneous or from trauma), and state of consciousness. (3) Indications for endovascular thrombectomy include: (i) The occlusion of a large vessel (internal carotid artery, M1 or M2 segment of the middle cerebral artery, tract A1 of the anterior cerebral artery, tract P1 of the posterior cerebral artery, basilar artery, and vertebral arteries). (ii) Possible detection of a mismatch between ischemic core and penumbra through perfusion neuroimaging in selected patients. *CT* computed tomography, *CTP* computer tomography perfusion, *CTA* computed tomography angiography, *MR* magnetic resonance

In patients with subtentorial brain structures, cerebral edema is a feared complication often causing a sudden deterioration of neurological conditions. The available evidence demonstrates the efficacy of suboccipital craniectomy in patients with cerebellar stroke who show clinical signs of compression of the brainstem structures despite the use of antiedema therapy [52, 53]; the intervention can be associated with ventriculostomy if the edema has caused obstructive hydrocephalus (COR I, LOE B) [8].

10.9.3 Glycemic State Management

Blood glucose changes are frequently found in patients with acute ischemic stroke admitted to the ICU; in some patients as a result of a preexisting diabetic condition, in others as a result of the stress of the acute disease [54].

It has been shown that prolonged hyperglycemia (blood glucose >155 mg/dL) is associated with a greater degree of functional dependence (mRS 2–3) (OR 2.73; 95% CI 1.43–5.24) and an increase in mortality (HR 3.79; 95% CI 1.79–8.10) 3 months after ischemic stroke [55].

Current recommendations include therapeutic interventions aimed at maintaining blood glucose values between 140 and 180 in patients with ischemic stroke in the acute–subacute phase [8].

10.9.4 Start of Antiplatelet Therapy

Early initiation of aspirin therapy has been shown to cause a mild but significant decrease in mortality in acute stroke patients in two large randomized controlled trials [56, 57]. Based on these results, the guidelines recommend the start of antiplatelet prophylaxis within 24–48 h of symptom onset [8]. However, any contraindications to the use of antiplatelet agents must be taken into consideration; for example, patients treated with Alteplase should not receive antiplatelet therapies for at least 24 h after the drug is infused.

10.9.5 Deep Vein Thrombosis Prophylaxis

Venous thrombosis is a frequent and often avoidable complication in patients with ischemic stroke during the hospitalization phase. Early mobilization and prophylactic antithrombotic therapy with heparin are effective in reducing the occurrence of DVT as suggested by recent guidelines. Intermittent pneumatic compression devices should be considered in patients with hemorrhagic infarction of the ischemic lesion or other conditions that contraindicate the use of heparin.

10.9.6 Initiation of Anticoagulation Therapy

The initiation or the resumption of an anticoagulant therapy may be a difficult decision in patients with very large strokes or who have experienced a hemorrhagic transformation of the ischemic lesion or have an increased risk for this complication (e.g., patients with very large ischemic lesions).

There are no data from randomized controlled trials regarding a safe timing of initiation of anticoagulant therapy in patients with extensive ischemic stroke and concomitant clinical indication to anticoagulant. The decision must be individualized for each patient on the basis of multiple factors, among which the most important are the size of the cerebral infarction, the general clinical conditions, the presence of hemorrhagic transformation, and the risk of new ischemic strokes.

10.9.7 Tracheostomy

Timing for performing tracheostomy in patients with severe stroke associated with respiratory impairment depends on the relationship between the benefits of the procedure (reduction of the risk of pneumonia associated with invasive ventilation, patient comfort, and dose reduction of sedatives) and the risk of exposing the patient to an unnecessary procedure.

A single-center study evaluated the effects of early tracheostomy in a sample of 60 severe stroke patients for whom the need for invasive ventilation was estimated for more than 14 days; the study showed a reduction in mortality during hospitalization in intensive care (10 vs. 47%) and at 6 months (27 vs. 60%) in the group of patients undergoing early tracheostomy. However, no differences were found between the two groups regarding the duration of stay in the intensive care unit [58].

The indication for tracheostomy remains a clinical decision and international guidelines do not provide specific indications to date.

10.9.8 Dysphagia Screening

Dysphagia is a very frequent complication in stroke patients: this symptom is due to an ischemic involvement of the cortical or brainstem areas involved in the control of pharyngeal musculature. Dysphagia is associated with a significant increase in the incidence of pneumonia and a longer duration of hospitalization [59, 60]. Studies that assessed the incidence of post-stroke dysphagia reported widely varying results, but it is estimated that approximately 50% of patients with ischemic stroke experience a certain degree of this symptom. In stroke patients, the aspiration of food material may, in some cases, not be associated with a cough reflex or other signs of distress; this event, called “silent aspiration”, causes a further increase in the risk of pneumonia.

The main guidelines recommend the assessment of swallowing function for all patients with ischemic stroke before starting feeding by mouth.

10.9.9 Neurorehabilitation

The beginning of early neuromotor rehabilitation in the intensive care unit has been associated with a reduction in the duration of hospital stay and in the incidence of pneumonia [61]; however, to date, the clinical evidence concerning the timing for the beginning of rehabilitation therapy is limited.

In 2015, a randomized controlled trial [62] evaluated the efficacy of early mobilization (within 24 h from admission to intensive care) compared to the usual starting time for rehabilitation in patients with ischemic and hemorrhagic stroke. The study did not provide results in favor of early rehabilitation in terms of functional recovery at 3 months, particularly for patients with hemorrhagic stroke. Furthermore, the study found no significant differences in the onset of complications related to immobilization between the two groups.

The current guidelines consider mobilization in patients with stroke to be essential, although they do not recommend the beginning of intensive rehabilitation in the first 24 h after stroke.

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