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Guidlines review

Acute stroke management - review of latest AHA/ASA guideline changes and their impact on modern stroke doctrine

2018 American Heart Association/American Stroke Association Guidelines Update

What is new in Acute Stroke Treatment?

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Abstract Acute stroke management has evolved over the past two decades, giving solid chance of recovery for most severe stroke survivors. The key to this shift of paradigm was interventional approach in stroke treatment, along with technology evolvement, which led to recanalisation strategies and Stroke-Unit concept development.

The latest set of recommendations from American Heart Association/ American Stroke Association (AHA/ASA) confirmed efficacy of mechanical thrombectomy in extended time window, making more patients eligible for interventional treatment. Intravenous thrombolysis remains golden standard and should be administered if indicated, regardless of endovascular treatment plans. Several changes are done in sections regarding pre-hospital management, hospital stroke teams, as well as some supportive aspects of stroke treatment. Some of those were debated in stroke community, resulting in publishing correction shortly after AHA/ASA Guideline's release.

Telestroke gain spotlight like no before, enabling decentralization of stroke care system.

Despite some points of controversy this version of AHA/ASA Guidelines continuous on broadening the spectrum of therapy for patients with acute ischemic stroke, enabling more patients to be eligible for critical procedures and interventions that could affect outcome. As with previous updates, new release is additionally changing the landscape of stroke treatment, in efforts of reaching the ultimate goal - to treat and beat stroke.

Keywords AHA/ASA Guideline, new recommendations, acute stroke treatment

Introduction

Over the past two decades, introduction of intravenous thrombolytic therapy (IVT) and Stroke Unit - based concept of stroke care has significantly improved the treatment outcome[1,2], moving stroke down the list from the fourth to fifth most common cause of death in the United States [3]. Nevertheless, it is still the most frequent cause of permanent disability, with escalating costs to the health system[3-6]. Short therapeutic time window and several contraindications for IVT have serious impact on patients eligibility, limiting treatment availability to up to 24% of the acute stroke patients [7]. However, in routine clinical practice, the actual number of stroke patients treated in this way is much lower, mainly due to prehospital delays [8–13]. Clinical reality is this: across the entire population of patients with stroke, treatment can be given to only a small minority (1–8%) of such patients[16], although experienced centers manage to administer intravenous alteplase to 20–30% of patients with ischaemic stroke within 3 hours[14,15]. Furthermore, IVT recanalisation rate is less than 30% in large proximal cerebral blood vessels occlusion[17,18]. Since approximately one third of acute ischemic strokes (AIS) are consequence of large vessel occlusion (LVO), it is clear that vast majority of patients with most severe stroke subtypes will not benefit from use of IVT. Consequently, endovascular treatment has been recognized and promoted as a promising additional or alternative treatment option for patients presenting with LVO[19,20], and further investigated as a potential first-line treatment or a part of combined (bridging) intravenous/intra-arterial therapy in larger randomized international multicentre trials[21-26].

Mechanical thrombectomy (MT) for AIS has evolved dramatically over the past decade, during which time results from 6 randomized controlled trials of early thrombectomy (MR CLEAN,1 EXTEND IA,2 ESCAPE,3 SWIFT PRIME,4 REVASCAT,5 THRACE,6)[21-26] and 2 of later

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thrombectomy (DAWN, DEFUSE 3) have established MT as the standard of care for patients with AIS harboring a LVO. Since results of aforementioned studies were published throughout 2015 and 2016, MT was not part of ASA/AHA guidelines published in 2013. This fact, together with accumulated novel data about IVT use and other therapeutic modalities in AIS treatment, mainly derived from meta analyses, urged the need for guidelines update.

At the 2018 International Stroke Conference in Los Angeles, the American Heart Association/American Stroke Association (AHA/ASA) released updated guidelines for the early management of ischemic strokes [27], based on more than 400 studies and containing revisions to the previous set of guidelines. Despite a mixed reception at the reveal of new guidelines due to some controversial recommendations and unusual turn of events in which the AHA/ASA rescinded the guidelines just a few month later, publishing correction without the agreement of the majority of the 2018 Acute Ischemic Stroke Writing Group[28], new recommendations made significant changes in therapy of AIS in several important aspects. Of those, maybe the most important is fact that, based on new recommendations, more patients are now eligible for acute procedures and medications following stroke. Though the list of new recommendations is stretching throughout various aspects of stroke treatment, two of those were highlighted by Guideline writing chair William J. Powers: extension of window for thrombectomies and expansion of eligibility for IVT use. In addition, several important points were outlined by members of the Board, mainly focusing on pre-hospital management and time-saving procedures and pathways.

Prehospital management and Hospital stroke teams

Early stroke symptom recognition is essential for timely contact of health care system, having significant impact on treatment outcome. Introduction of IVT further emphasized importance of time and knowledge about stroke symptoms in general population. Educational campaigns, media coverage and other forms of edification provided by medical professionals and public health care leaders were recognized a long time ago as important tool in raising of public averseness, being part of past recommendations. New guidelines keeps this issue in focus by adding high COR (I) and LOE (B-R) marks. New recommendations include optimization of stroke averseness campaigns according to age, sex and minority status, due to variations in effect of public interventions, as well as importance of sustained effort in continuous public education[29].

Attempt to achieve door-to-needle time (DTN) of ≤ 60 minutes in more than half of AIS patients treated with IVT was prompted once again in new guidelines, gaining revision of prior recommendation, and including new recommendation regarding reasonable efforts in reaching of 45 minutes time frame in more than 50% of cases. Results of studies analyzing DTN timing from 2003. showed constant decrease in median DTN time after establishing the time goal[30,31], reaching median DTN time of 56 minutes, with 30,4% treated within 45 minutes after hospital arrival in cohort study conducted in 2014 and 2015 [32].

Several new recommendations are given regarding telestroke/teleradiology evaluation of AIS patients. Although telephone consultations in decision making processes for patients with AIS proved safe and feasible[33], use of telemedicine networks (including teleradiology) further improved patients selection, resulting in statistically significantly more accurate IVT eligibility decision making compared to telephone consultations[34]. Use of telephone consultations for patients with acute stroke is recommended if there is no in-hospital stroke team or telestroke system available[33].

Meta-analysis and systematic review of safety and efficacy of IVT use through telestroke networks showed no significant differences in complication rates (symptomatic intracerebral hemorrhage (SICH)), mortality and functional independence at three months comparing to stroke-center managed patients[35]. It also proved to be reasonable option for triaging patients who may be eligible for interfacility transfer when considering mechanical thrombectomy. A retrospective observational study that compared clinical outcomes of endovascular treatment (EVT) between patients transferred after teleconsultations and those directly admitted to tertiary stroke center found similar rates of reperfusion and favorable clinical outcome, with lower rates of SICH and mortality in transferred patients, suggesting that use of telestroke networks may be beneficial for triage of patients eligible for transfer and following EVT[36].

Brain imaging and intravenous thrombolytic therapy

In the vast majority of cases of IVT use, non-contrast CT (NCCT) will provide the necessary information to make acute management decisions. It has been shown that the NCCT is profitable primarily for the detection of intracranial bleeding and avoiding antithrombotic treatment in these patients[37].

Recent guidelines provided new recommendations regarding several aspects of brain imaging, including early signs of ischemia on NCCT, use of MRI and multimodal imaging in acute settings. Early signs of ischemia on non-enhanced brain CT include tissue hypoattenuation, lesion swelling, and arterial hyperattenuation from occlusive thrombus. New recommendations suggest that the presence of early signs of ischemia, particularly presence of hyperdense MCA sign and tissue hypoattenuation should not be used as a criterion to withhold IVT use from patients who otherwise qualify[27].

The third international stroke trial (IST-3) addressed this issue and concluded that some early ischemic and pre-existing signs were associated with reduced independence at 6 months and increased rates of SICH, although no interaction was noted between hyperdense artery signs and effects of IVT use on aforementioned outcomes[38]. Due to increase in absolute risk for SICH in presence of some combinations of signs (e.g. both old infarct and hyperdense artery sign), authors suggest

consideration of pre-existing signs in addition to early signs of ischemia in assessment of eligibility for IVT use.

Several other studies also showed that there is no statistically significant correlation between clinical outcomes after IVT treatment and presence of hyperdense MCA sign on baseline NCCT. In the NINDS rtPA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months, measured by any of the 4 clinical scales (modified Rankin Scale [mRS], National Institute of Health Stroke Scale [NIHSS], Barthel Index [BI] and Glasgow Outcome Scale [GOS]), or death[39, 40]. There were no sufficient data from RCTs regarding identification of threshold for acute CT hypoattenuation severity or extent that might affect treatment response, and it should not be used as a criterion to withhold IVT for patients otherwise eligible for treatment[27].

Use of MRI before thrombolysis is not recommended in routine clinical practice[27]. However, patients with cerebral microbleeds (CMB) could be in higher risk of SICH after IVT treatment[41,42], and MRI could have potential role in decision making process in this subgroup of patients. Regarding this issue, two new recommendations are given. In otherwise eligible patients who have had a previously demonstrated small number (1–10) of CMBs on MRI, administration of IVT is reasonable (class IIa and level of evidence B-NR). In otherwise eligible patients who have had a previously demonstrated high burden of CMBs (>10) on MRI, treatment may be associated with an increased risk of SICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit reasonable (class IIa and level of evidence B-NR)[27].

Risk of initiating antiplatelet therapy within 24 hours of thrombolytic therapy remained unknown in new set of recommendations[27]. A retrospective analysis found no increased risk of SICH with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or initiation >24 hours[43]. However new studies are needed to give more precise answers to the question of when to start antiplatelets after thrombolytic therapy. If considering early initiation of antiplatelet therapy (< 24h after IVT), decision should be individually based, balancing risk and benefit[27].

Except for recombinant tissue plasminogen activator (rtPA) and tenecteplase there is no evidence that other thrombolytic agents are effective. The benefit of IV fibrinolytic agents other than alteplase and tenecteplase is unproven; therefore, their administration is not recommended outside a clinical trial[27]. In study of Huang et al. tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase[44].

In a recently published study tenecteplase, given as single IV bolus at a dose of 0.4 mg/kg, failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase[45]. Trial included 1100 patients with minor neurological impairment (median NIHSS score 4) and no LVO.

Sonothrombolysis is not recommended as adjuvant therapy with IVT. So far, there is no sufficient data to support use of sonothrombolysis in patients with AIS [27].

Mechanical thrombectomy

Several important changes and novelties on endovascular treatment modalities were anticipated in order to clarify uncertainties about target population and timeframe for EVT procedures. Since former version of guidelines were published in 2013., prior to the six positive "early window" mechanical thrombectomy (MT) trials (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFTPRIME, THRACE), MT was considered as reasonable alternative for IVT in selected patients. In 2015. Focused update on Acute Ischemic Stroke and Endovascular treatment was released[46], intruducing EVT with stent retriever in all eligible patients with causative occlusion of ICA or proximal (M1) MCA with highest Class (I) and Level of Evidence (a). Since then, several clinical and population-based studies confirmed safety and efficacy of MT in proposed 6-hours window, while two trials (DAWN and DEFUSE 3) showed a clear benefit of "extended window" MT for selected patients with large vessel occlusion who could be treated out to 16 - 24 hours[47, 48].

Use of IVT in all eligible patients is still recommended, even if EVT is considered. Since benefits of recombinant tissue plasminogen activator (rtPA) are time-dependent, treatment for eligible patients should be initiated as quickly as possible (even for patients who may also be candidates for MT)[27]. However, because outcome after EVT is also time dependent, any cause for delay, including observation after IVT to assess for clinical improvement should be avoided [27, 32]. All eligible patients should be treated within six hours time-window with no special remarks regarding elderly patients, but with consideration of comorbidities and risks in decision making for MT[49-51]. No perfusion imaging (CT-P or MR-P) is required in these patients.

In a surprisingly radical move for the usually more glacial pace of wide-ranging guideline overhaul, new guideline expanded the treatment window for MT within hours of release of supporting data trial. Just a few hours after publishing, data from DAWN and DEFUSE 3 trials were incorporated into new guidelines, expanding time window for MT up to 16 hours in eligible patients, and up to 24 hours after symptom onset in selected patients[47,48].

The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria for selection of patients with anterior circulation LVO for MT within 6 to 16 hours time frame from last seen well. Trial results showed a benefit in functional outcome at 90 days in treated group (mRS score 0-2, 44.6% versus 16.7%; RR, 2,67; 95% CI, 1.60-4.48; P<0,0001)[27,47]. In subgroup analysis, benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not[27].

Clinical-imaging mismatch, represented as combination of NIHSS score and findings on CT-P or Diffusion-Weighted MRI (DW MRI) were used as inclusion criteria to select patients with anterior circulation LVO eligible for MT in the DAWN trial. Time window for MT in this study was between 6 and 24 hours from last seen normal. Similar to DEFUSE 3, this trial demonstrated ben-

efit in functional outcome at 90 days in the treatment group (mRS 0-2, 49% versus 13%; adjusted difference, 33%; 95% CI, 21-44;)[48].

Based on results of those trials, MT with stent retriever is recommended in selected patients within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria. Use of MT is reasonable therapeutic option in selected patients between 16 and 24 hours of last known normal who have anterior circulation LVO and meet other DAWN eligibility criteria. Since DAWN and DEFUSE 3 are the only randomized controlled trials (RCTs) showing benefit of MT after six hours from symptom onset, strict adherence to the eligibility criteria from one of these trials in patients selection is recommended in everyday clinical practice[27].

Several, mainly technical and practical aspects of EVT and concomitant clinical management were revised or newly addressed in latest guidelines, but are beyond scope of this article. For more details refer to ASA/AHA 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke[27].

Conclusion

New AHA/ASA guidelines introduced several new recommendations regarding various aspects of acute stroke treatment, while even more of them received some form of revision according to newly acquired data. Introduced as Update of previous version, new guideline confirmed important role of EVT in acute stroke management, delivering set of recommendations covering different aspects of this issue. Time frame for endovascular intervention has been significantly prolonged, enabling much more patients to be eligible for intervention. Nevertheless, IVT remains cornerstone of acute treatment, gaining broaden eligibility criteria, and remaining first-choice therapy in all eligible patients with AIS.

Besides abovementioned, all others sections of guidelines experienced changes in some level, in order of more efficient and beneficial stroke care, with ultimate goal of lowering the risk of disability from stroke. Importance of getting to hospital effectively and delivering care quickly was emphasized once again by setting the new set of goals regarding door to needle time.

Telestroke gain spotlight like no before, enabling decentralization of stroke care system.

Despite some points of controversy and opinions that new guideline failed to fully recognize potential role of EVT in patients with large vessel occlusion, this version continuous on broadening the spectrum of therapy for patients with AIS, enabling more patients to be eligible for critical procedures and interventions that could affect outcome. As with previous updates, new release is additionally changing the landscape of stroke treatment, in efforts of reaching the ultimate goal - to treat and beat stroke.

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Sažetak

Terapija akutnog ishemijskog moždanog udara (AIMU) je značajno napredovala u poslednje dve decenije, omogućivši time značajno povoljnije šanse za dobar funkcionalni oporavak kod većine pacijenata. Ključni korak u promeni paradigme predstavljalo je uvođenje intervencionalističkog pristupa, podržano razvojem tehnologije, čime je omogućena primena rekanalizacionih procedura i multidisciplinarni pristup lečenju sa Jedinicom za moždani udar kao stožerom koncepta lečenja.

Poslednje preporuke za lečenje AIMU od strane Američke asocijacije za srce/Američke asocijacije za moždani udar (AHA/ASA) potvrdile su efikasnost mehaničke trombektomije u produženom terapijskom prozoru, učinivši je dostupnom većem broju pacijenata. Intravenska trombolitička terapija ostaje zlatni standard u terapiji AIMU i preporučuje se njena primena kod svih pacijenata koji ispunjavaju kriterijume za primenu, bez obzira na planirane sledstvene endovaskularne intervencije. Takođe, nekoliko novih preporuka posvećeno je aspektima prehospitalnog lečenja, organizacije hospitalnog lečenja, kao i u drugim domenima terapije. Neke od izmena su bile predmet rasprava u stručnim krugovima, sa posledičnim izmenama pojedinih preporuka nedugo nakon zvaničnog predstavljanja novog Vodiča. Telemedicina je dobila daleko značajniju ulogu nego ranije, omogućavajući decentralizaciju sistema lečenja. I pored pojedinih kontraverzi koje su pratile objavljivanje poslednje verzije Vodiča, nove preporuke nastavljaju sa napretkom u terapijskom pristupu lečenju AIMU, na taj način dajući šansu za dobar oporavak većem procentu pacijenata, na putu ka konačnom cilju, potpunom izlečenju.

***Ključne reči**: AHA/ASA, Vodič, nove preporuke*