ASK THE EXPERTS

How Do You Manage Cases With Low ASPECTS?

A panel of experts weighs in on the impact of specific clinical measures to guide treatment decisions and predict outcomes.

WITH MAYANK GOYAL, MD; AQUILLA S. TURK, DO; MICHAEL FROEHLER, MD, PHD; AND TUDOR G. JOVIN, MD

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In light of all the recent trials, the American Heart Association/American Stroke Association guidelines changed in 2015, with endovascular thrombectomy becoming the standard of care for patients with large vessel occlusions (LVOs) in the anterior circulation and an Alberta Stroke Program Early CT Score (ASPECTS) > 5. Subsequently, the HERMES collaboration was created, of which I am the Chair, and includes patient-level imaging and clinical database from seven trials (MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE). We created an anonymized master imaging database, and all of the imaging studies were reread centrally (the imaging readers were blinded to the source trial, the arm the patient was randomized to, final outcome, etc). The results of this analysis, which were presented at the European Stroke Organisation Conference in 2017 and will soon be published, show a benefit associated with endovascular thrombectomy even in patients with low ASPECTS (moderately large core). But, how does this information translate to day-to-day practice and decision-making?

Thomas Bayes, an 18th century English statistician, philosopher, and Presbyterian minister, formulated a theorem that later came to be known by his name, the Bayes theorem.[1] This theorem, in my opinion (and in my practice), is central to decision-making in the situation of low ASPECTS. A brief video explaining the theorem can be found at http://bit.ly/2j14vL6. So, how does it apply in practical terms?

In the process of decision-making in acute stroke, any single factor—whether it is age, severity of stroke symptoms, ASPECTS, time from onset—cannot be taken in isolation but rather in conjunction with each other. Therefore, if a 45-year-old patient presents with a National Institutes of Health Stroke Scale (NIHSS) score of 18 at 90 minutes from onset, the way I think about the problem (even before seeing the imaging) is totally different than if the patient were a 93-year-old at 5 hours from onset with a NIHSS of 21 being transferred from a nursing home. These factors have a complex interplay with each other and influence the overall outcome. In general, younger patients who present early after onset of symptoms have a higher likelihood of doing well despite having a large core. The other factor that can influence decision-making in the real world is the patient's (and their family's) expectation of outcome. Of course, these have a cultural overlay, but overall, in my experience, many older patients do not want to live severely disabled and may choose quality

over quantity of life. When explicitly stated, these factors should also be taken into account for decision-making.

In the HERMES collaboration, modified thrombolysis in cerebral infarction (mTICI) 2b/3 reperfusion was < 70%. With improvements in technique, technology, and training, our overall quality of reperfusion keeps improving. In fact, I believe we should not be looking at mTICI 2c/3 reperfusion. Additionally, with the data for the "time is brain" concept, most centers have much higher efficiency and better workflow than what was accomplished in the trials. These two factors are influencing our understanding of "core" and its relationship to outcome. We are increasingly seeing patients with so-called core tissue on CT perfusion studies that does not show signs of cellular death on follow-up after efficient, high-quality reperfusion. There is also the possibility of selective and patchy neuronal loss rather than pan necrosis after efficient endovascular thrombectomy that influences outcome.

To summarize, data from the HERMES collaboration shows a benefit in patients with low ASPECTS. In my practice, I use Bayesian decision-making in these situations (with consideration of many factors such as age, time from onset, severity of stroke, expectation of outcome, and imaging features). With improvements in efficiency and quality of reperfusion, our understanding of infarct "core" will likely further evolve.

1. Thomas Bayes. Wikipedia. https://en.wikipedia.org/wiki/Thomas_Bayes. Accessed November 20, 2017.

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ASPECTS is a widely used tool devised to quantify the extent of early ischemic changes in the middle cerebral artery territory on noncontrast CT imaging. This has also been applied to perfusion and diffusion imaging with good results. As you can tell from this description, the tool is limited to those patients with middle cerebral artery occlusions. There is further limitation in inter- and even intrareader variability, especially in community settings. Despite these limitations, ASPECTS is still a useful and easily applicable tool for prognosis assessment in acute stroke treatment and to help guide acute treatment decisions.

Numerous randomized trials and pooled meta-analysis (HERMES) of data from these trials have shown that mechanical thrombectomy is superior for treating acute ischemic stroke secondary to a LVO.[1] These groundbreaking trials mainly enrolled patients presenting with severe stroke symptoms manifested by a high NIHSS score and imaging showing a LVO without a large infarction present. In fact, the HERMES data showed that < 10% of patients had an ASPECTS ≤ 5. The data from HERMES did suggest a trend toward thrombectomy patients having a better chance of a good outcome, but this was not statistically significant. Newer reports suggest that patients undergoing thrombectomy have a higher chance of achieving a good functional outcome and lower chance of mortality or hemicraniectomy than if they do not have the procedure.[2,3]

In our practice, we use ASPECTS when discussing cases with referring clinicians. However, for therapeutic decision-making, we always review the CT/CTA/CT perfusion imaging to determine the penumbra. It is critical to determine whether the penumbral region is eloquent and its relevance to the clinical symptoms so that we can detect a clinical–imaging mismatch. Finally, and perhaps most importantly, is setting expectations for the patient's family. Infarct volume at baseline has been shown to be a strong and independent predictor of clinical outcome at 90 days, as well as the likelihood of developing a symptomatic intracranial hemorrhage. The rates of good functional outcomes in this population are lower than those achieved in trial settings and in the majority of patients in our everyday practice. However, relative to those not undergoing thrombectomy, there is likely a gain.[2,3] So, if there is a large infarction present with an eloquent region at risk, even if it is small, then it is appropriate to intervene.

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723-1731.
2. Mourand I, Abergel E, Mantilla D, et al. Favorable revascularization therapy in patients with ASPECTS ≤ 5 on DWI in anterior circulation stroke [published online October 27, 2017]. J Neurointerv Surg.
3. Desilles JP, Consoli A, Redjem H, et al; ETIS (Endovascular Treatment in Ischemic Stroke) Research Investigators. Successful reperfusion with mechanical thrombectomy is associated with reduced disability and mortality in patients with pretreatment diffusion-weighted imaging-Alberta Stroke Program Early Computed Tomography Score ≤6. Stroke. 2017;48:963-969.

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The current guidelines state that endovascular treatment is indicated if the ASPECTS is 6 or better. This is based on the five randomized controlled trials published in 2015. However, some patients with relatively poor ASPECTS may still have a reasonable chance of recovery; they simply were not included in these large trials. Several retrospective studies have shown that good outcomes are still achievable in patients with ASPECTS ≤ 5, although the likelihood of good outcome appears to be lower than in patients with better ASPECTS. Furthermore, the recently published DAWN trial did not use ASPECTS for patient selection, but rather used perfusion imaging to identify patients with significant salvageable brain tissue.

Based on the available studies, as well as my experience, we typically will use ASPECTS as one element in the information set used to make a thrombectomy decision. Other key information includes patient age, baseline functional status, comorbidities, location of occlusion, perfusion imaging, and patient preference. When considered in this context, poor ASPECTS does not necessarily mean that I will not offer thrombectomy, but it certainly is one important piece of information. For instance, a young patient with a good functional baseline and no other health concerns might be a candidate for endovascular treatment despite an ASPECTS < 6, although I would still caution the family and the rest of the treatment team that an excellent outcome is unlikely.

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One of the biggest changes in my practice, brought about by the results of the recent randomized trials in endovascular stroke treatment, has been the way I approach patients with low ASPECTS in the hyperacute (0–6 hours) time window. I have always been a staunch believer in endovascular therapy for acute ischemic stroke and have been treating patients long before the randomized trials. Before the randomized data became available, like many of my like-minded peers, I practiced based on observations from single-arm studies showing that patients with low ASPECTS have poor overall outcomes, and I was therefore reluctant to treat such patients. An analysis of the database including well over 1,000 patients treated at our center (University of Pittsburgh Medical Center) since 2000, but prior to the publication of the five randomized thrombectomy trials in 2015, would have revealed that the median ASPECTS was 8 in patients treated with thrombectomy.

My approach to ASPECTS has evolved over time, from being considered the single most important factor for patient selection to only one of several key factors, the other critical factor being age. The basis for this approach has been knowledge gained from several studies including one conducted at our own center, showing that with increasing age, a lower qualifying infarct volume becomes necessary to obtain a good clinical outcome even with high-quality reperfusion. Guided by this principle in clinical practice, my colleagues and I were generally selecting patients based on an age-adjusted ASPECTS paradigm; patients were considered candidates for thrombectomy if their ASPECTS was greater than or equal to the first digit of their age. For example, we would treat an octogenarian if their ASPECTS was ≥ 8, but would lower the cutoff for a 50-year-old patient to an ASPECTS of 5. Nonetheless, because of concerns about harm in the form of symptomatic intracerebral hemorrhage and accelerated malignant edema, an ASPECTS of 5 or its equivalent, greater than one-third middle cerebral artery hypodensity, constituted the lower limit of baseline infarct I was willing to treat regardless of the patient's age.

With the five published randomized trials, along with HERMES, in 2015, we now had the individual patient-level pooled analysis from these trials. Once endovascularly treated patients could be compared to those treated with standard medical therapy alone (which, in the majority of these cases, included intravenous tissue plasminogen activator), several critically important insights became apparent. First, just like age, ASPECTS

emerged as a prognostic factor, but not a treatment effect modifier. Treatment benefit is maintained across the entire spectrum of ASPECTS categories, which is owed to the fact that although patients with low ASPECTS tend to have poor outcomes overall, outcomes in medically treated patients with poor ASPECTS are even worse. This suggests that most patients with large baseline infarcts still have some salvageable brain tissue. Restoration of flow in the ischemic area results in brain tissue salvage, which, even in this category of patients, translates into improved outcomes compared to nontreated patients.

In keeping with this contention, a recently completed HERMES-based pooled analysis that included over 1,800 patients from all six completed randomized trials with patients enrolled in the early time window indicated that the benefit of thrombectomy is present even in patients with a baseline ASPECTS of 0 to 4 as ascertained by CT or diffusion-weighted MRI. More importantly, even though there was a higher proportion of symptomatic intracerebral hemorrhage in the endovascular group of this study compared to the control group, there was no signal of overall harm when patients with low ASPECTS were treated with thrombectomy compared to medically treated patients.

Another major insight emerging from the HERMES study is that in the time window in which most patients from the HERMES data set were randomized (0–6 hours), clinical outcomes from thrombectomy are extremely time sensitive. Furthermore, other studies have suggested that within this time window, the incidence of patients with very low ASPECTS (0–5) is in fact quite low (approximately 15%). Therefore, time-consuming steps aiming to precisely determine ASPECTS (ie, a trip to the CT scanner or a repeat CT of the head to determine the ASPECTS in a transferred patient) may result in harm through delay in reperfusion without a clear benefit, as the only consequence of obtaining the ASPECTS would be to exclude a minority of patients from treatment who current evidence suggests may benefit from thrombectomy and are unlikely to derive harm from it.

On the other hand, patients with higher ASPECTS who constitute a clear majority of thrombectomy candidates presenting within 0 to 6 hours are unquestionably harmed by delays in reperfusion related to additional imaging. For that reason, in order to not prejudice the majority of patients with LVO stroke presenting within 6 hours of symptoms onset by introducing unnecessary delays due to imaging, in my current practice, I use a plain head CT regardless of when this CT was obtained in relationship to thrombectomy initiation and do not resort to repeating a head CT for the purposes of ASPECTS determination in transferred patients as long as treatment can be initiated within 6 hours.

I believe that a randomized trial to definitively clarify the benefit of thrombectomy in patients with proximal LVO presenting within 0 to 6 hours is warranted. However, until such a trial contradicts the current state of knowledge derived from pooled analyses of randomized trials that indicate no harm and a high likelihood of benefit from thrombectomy in patients with low ASPECTS overall, even those presenting directly to the endovascular center, I do not exclude patients from thrombectomy based on baseline imaging findings (including ASPECTS) alone.

With time, the proportion of patients with salvageable brain diminishes, and therefore the benefit of more precisely delineating the amount of infarct in relationship to amount of tissue at risk (ie, determining whether salvageable brain still exists) offsets the harm derived from the time expenditure necessary for obtaining this information. One can argue where the time cutoff should be, but available data converge toward 6 to 8 hours. Beyond this time frame, data from DAWN suggest an overwhelming benefit of thrombectomy in patients with severe clinical deficit and small baseline infarct volumes, which generally correspond to ASPECTS ≥ 7. Therefore, I generally do not perform thrombectomy in patients beyond 8 hours from the time last seen well with ASPECTS < 7 or 8 (depending on age, NIHSS score, and other factors). However, the lower limits of ASPECTS at which benefit still exists beyond the 6-hour time window remains to be established by future studies.

In summary, I approach ASPECTS differently depending on the time window in which the patient presents. In the 0 to 6-hour time window, I attribute increasingly less relevance to ASPECTS and increasingly emphasize workflow measures aimed to increase the speed of reperfusion. In this time window, in which the vast majority of patients still have reversible brain ischemia, I do not exclude patients from treatment based on imaging (including ASPECTS) alone and take into account a multitude of other factors in my decision to offer treatment, even if the patient has a very low ASPECTS. Beyond the 6-hour time window, I use an ASPECTS cutoff of 7 or 8 depending on the patient's age and the estimated presence of mismatch, which I primarily ascertain based on the patient's NIHSS score. ■