Synapse
a clinical resource
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The Benefits of 3D Vision

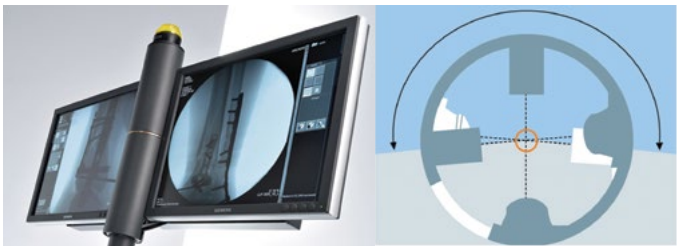
Tushar M. Goradia, MD, PhD

Headed back to California from a recent medical conference in Baltimore, I had just passed through the millimeter-wave detector at BWI Airport and was awaiting clearance following TSA inspection of my briefcase. Like fellow travelers (since my cell phone was separated from me) there was not much else to do but witness the TSA agent screening bags via x-ray. I watched the x-ray video monitor and wondered how he could identify a weapon among items superimposed on a flat x-ray image. Although the x-ray was colorized to help differentiate item density it was nonetheless an imperfect 2D projection of objects piled on each other. Despite this limitation, the TSA officer was undoubtedly well-trained to sight potential danger among the mishmash of items in purses and carry-on bags, just from viewing the 2D projection.

Now imagine how much easier it would be for TSA if they had a 3D visualization of contents in bags. In other words, they would be able to see the objects as if the bag itself were invisible and each object visibly stood apart in three dimensions. The object that appeared as a narrow elongated triangle in two dimensions, looking suspiciously like the tip of a knife, could quickly be resolved as a harmless carrot.

Up until recently, most neurosurgeons have had no good alternative to the similar challenge of visualizing a patient's spine anatomy during surgery. When introducing screws into vertebrae for fusion or fixation surgery, surgeons were limited to viewing only a 2D maximum-intensity-projection of the screw in the patient's spine.

Enter the Siemens Orbic 3D, which is a state-of-the-art x-ray machine that allows visualization in 3D. Surgeons at Mercy San Juan Medical Center are employing this technology to make surgery safer and faster. This tool is particularly helpful for otherwise "blind" procedures in which a surgeon treats a patient



by directing therapy into closed compartments, such as the interior of a vertebral body. Our neurosurgeons have been utilizing the Orbic 3D to help cannulate pedicles with pedicle screws.

Pedicle screw cannulation can be challenging because of the narrow corridor which separates bone from neural tissue. Traditionally, this has been done using a combination of haptic (tactile) feedback and 2D x-ray guidance. However, this requires time and x-ray exposure to assure good positioning of the screws. When the spine is seen in 3D, visualization of the exact location of the screws is near-perfect. This allows modification of the screw trajectory, if needed, to improve the spinal construct.

In a typical scenario, the surgeon places screws in all the pedicles that require screw fixation, and then a "spin" is performed wherein the C-shaped machine automatically rotates about the long axis of the patient, focused on the spine as its target. The resulting image is then reviewed in orthogonal cross-sections to assess screw placement. If an improvement in screw placement can be made, the surgeon can do so while he still has the surgical site exposed.

All interventions in medicine are prone to error. We strive to prevent error with the latest technology that provides concurrent x-ray and computer feedback. Technologies such as the Orbic 3D pave the way for robotic surgery of the future—and perhaps even enhanced baggage screening. ■

Tushar M. Goradia, MD, PhD

Dignity Health™
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Sports-Related Concussions

Kenneth Cheung, MD

Management of sports-related concussions is an important and topical issue among athletes and clinicians alike as we strive to provide the best medical care for our patients. The purpose of this article is to review the basics of a concussion and to review the current clinical guidelines of the management of this all too common brain injury.

In March 2012, the American Academy of Neurology released updated clinical guidelines regarding sports-related concussions based on a thorough, evidence-based review of the current literature. This replaces the prior 1997 guidelines that used a grading system for concussive injuries that has since fallen out of practice. Many of the recommendations are discussed below, but for those interested, please learn more on the AAN website (www.aan.com/practice/sports-concussion-toolkit/).

A concussion is a form of mild traumatic brain injury and a clinical syndrome resulting from biomechanically induced alteration of brain function. It is estimated that anywhere from 1.6 to 3.8 million concussions result from sports or recreational activities and almost 9% of all US high school sports injuries involve concussions.

The symptoms following a concussion are diverse, encompassing somatic, cognitive and behavioral domains. Some of the most common symptoms include headaches, fatigue, dizziness, nausea, balance issues, irritability, difficulties with sleep and an inability to concentrate. While the vast majority of concussions are self-limiting, prolonged symptoms can occur, and the long-term effects of multiple concussions are unknown.

The severity and duration of symptoms that result from a concussion can vary on an individual basis, and there is no set timeline for recovery or return to play. Important factors to consider are age, previous concussions, headache history, prior mood or sleep disorders and baseline learning disabilities.

Pre-participation counseling for school officials, athletes and their parents by an experienced, licensed, healthcare provider (LHCP) regarding the risks and consequences of head injury is recommended prior to participation in athletics. This may include signing a concussion information sheet for both athletes and parents prior to participation.

Even with an experienced team physician, recognizing an acute concussion can prove to be very challenging as there is no single test or study to definitively diagnose a concussion. Standardized symptom checklists and the Standardized Assessment of Concussion (SAC) have been shown to be useful in the early diagnosis of concussion. It is ultimately a clinical diagnosis, and in addition to a thorough history and neurological exam, evaluation of a concussion may also incorporate balance assessment and neurocognitive testing administered by an experienced neuropsychologist. Imaging should be utilized to rule out more catastrophic head injuries, if suspected.

It is recommended that any athlete who is suspected of having a concussion be removed immediately

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Sports-Related Concussions—continued from page 2

Table 1 Graduated return to play protocol

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% maximum predicted heart rate	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, e.g. passing drills in football and ice hockey	Exercise, coordination and cognitive load
5. Full contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

from the field of play, and should not return until cleared by a LHCP who is trained in the evaluation and management of concussion. In order to diminish the risk of recurrent injury, athletes should not return to practice until the concussion has resolved. Sideline coaches and trainers should follow the rule of thumb: "No same-day return-to-play."

The cornerstone of concussion management is some degree of physical and cognitive rest until acute symptoms resolve, and then a stepwise Return-to-Play protocol prior to medical clearance (see Table 1). The extent and length of time for rest can vary on an individual basis, and an experienced clinician can assist with these decisions. There is no evidence that absolute cognitive and physical rest is beneficial after a concussion, and modified work or school accommodations may be advisable to assist the athlete in the subacute period. In general, high school athletes and younger populations should be treated more conservatively than older athletes as they have been shown to have longer recovery times.

"When in doubt, sit them out!"

There is still much to learn about concussions, how to diagnose and manage them effectively, especially in the younger population, and their long-term repercussions. ■

Stroke Prevention in Atrial Fibrillation in the Era of Novel Oral Anticoagulants

Asad A. Chaudhary, MD

There are 795,000 strokes every year in United States. Every 40 seconds someone has a stroke and every four minutes someone dies from it. Stroke is the leading cause of adult disability. More than 80% of strokes are ischemic and the rest hemorrhagic. The common etiologies of ischemic stroke are large vessel atherosclerosis, small vessel disease, cardioembolism and others that include arterial dissection, hypercoagulable disorders and cryptogenic.

It is estimated that 10-30% of ischemic strokes are cardioembolic. In the 1990s the SPAF trials, EATF study group and SIFA investigators established that warfarin is superior to aspirin for primary and secondary stroke prevention in atrial fibrillation. Warfarin provides ~60% risk reduction vs. ~10% with aspirin. The disadvantages of warfarin include narrow therapeutic window, frequent monitoring, increase ICH risk, drug/food interactions, genetic variations in response, slower onset of action, bridging, variability in generic preparations, dependence on hepatic function and only 60-70% TTR (Time in Therapeutic Range). The cited advantages, on the other hand, include extensive experience, once daily dosing, long half life, regular monitoring, available antidotes and low cost.

The RE-LY trial, published in 2009, compared the direct thrombin inhibitor, dabigatran (Pradaxa) to

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warfarin for stroke prevention in non-valvular atrial fibrillation. The rate of stroke or systemic embolism was 1.1% per year on dabigatran 150mg twice daily, 1.5% per year on dabigatran 110mg twice daily, and 1.7% per year on adjusted dose warfarin. Dabigatran 150mg dose prevented more embolic events than warfarin with a similar risk of bleeding. Dabigatran 110mg dose was non-inferior to warfarin at prevention of stroke or systemic embolism, but with less risk of major bleeding. Unfortunately the FDA only approved 150mg and the untested 75mg dose for patients with renal dysfunction. The reason is not very clear but likely to discourage non-inferior 110mg dose over superior 150mg dose.

The RELY-ABLE study, a 4 year follow-up of dabigatran, has shown results similar to RE-LY. The disadvantages of dabigatran are twice daily dosing, increase gastrointestinal bleeding, possible myocardial infarction risk, dyspepsia, no reliable monitoring, renal dose adjustment (80% renally excreted), cost and lack of known antidote. The shorter half life of 12-17 hours compared to warfarin somewhat counterbalances the lack of antidote for now. The mortality from intracerebral hemorrhage (ICH) in RE-LY was 35% with dabigatran vs. 33% with warfarin. Early research of a fully humanized monoclonal antibody fragment Fab has been completed and will be going into phase I clinical trial soon. For now, dialysis remains the only reliable way to reverse it. Advantages are fixed dosing, no monitoring, rapid onset, decrease ICH risk, few drug/food interactions and no bridging.

The ROCKET-AF trial, published in 2011, showed that the factor Xa inhibitor, rivaroxaban (Xarelto), administered 20mg once daily was non-inferior to dose-adjusted warfarin in the prevention of ischemic stroke and with similar rates of major and clinically relevant non-major bleeding. Rate of stroke and embolism was 2.1%/yr with rivaroxaban vs. 2.4%/yr with Coumadin and hemorrhagic strokes 0.5%/yr vs 0.7%/yr respectively. This study had patients with higher CHADS2 scores but only 54% in the warfarin arm in TTR. The notion about rebound with rivaroxaban has now been refuted. Its disadvantages are no long term effectiveness data, dosing restriction for renal dysfunction (36-45% renally excreted) and cost. Advantages are fixed daily dosing, no monitoring, decrease ICH risk and few drug/food interactions.

More recently, apixaban (Eliquis), another factor Xa inhibitor, was approved by the FDA based on AVERROES and ARISTOTLE trials. It was clinically superior to warfarin, safer and the only new anticoagulant with additional mortality benefit. Rate of stroke and systemic embolism was 1.3%/yr with apixaban vs. 1.6%/yr with warfarin and the rate of major bleeding was 2.13%/yr vs. 3.09%/yr, respectively. The disadvantages are twice daily dosing, patient adherence, no long term effectiveness or safety data, no antidote yet and cost. The advantages are fixed dosing, only 25-30% renally excreted, no monitoring, rapid onset of action, few drug/food interactions and decreased bleeding.

Most recently, ENGAGE AF-TIMI 48 trial results for edoxaban, another Factor Xa inhibitor, showed it to be at least as effective as warfarin in preventing stroke and systemic embolism with a better safety profile. The rate of stroke and systemic embolism was 1.5%/yr with warfarin vs. 1.18%/yr with edoxaban and the rate of major bleeding was 3.43%/yr vs. 2.75%/yr, respectively. Other Factor Xa inhibitors like betrixaban are also on the horizon.

There is some evidence now that these Factor Xa inhibitors can somewhat be reversed with PCCs (Prothrombin Complex Concentrates). Additionally, PRT 4445 (andexanet alfa), a recombinant, modified factor Xa inhibitor molecule, passed phase 1 testing in 32 health volunteers. Results of a phase II trial were promising and further trials are anticipated.

In summary, dabigatran 150mg BID and apixaban 5mg are the only two drugs superior in efficacy for ischemic strokes when compared to warfarin (Coumadin) and rivaroxiban (Xaralto). It is paramount that patients with atrial fibrillation with high CHA2DS2 VASc scores and favorable HAS BLED scores are placed on anticoagulation. Despite the availability of safer and better new agents, 80% of patients continue to be on warfarin. Physicians, and stroke neurologists in particular, should consider these newer agents as the first line for stroke prevention in non-valvular atrial fibrillation.

For references, comments or questions please email Dr. Chaudhary at MercyNeuro@DignityHealth.org ■

Stenting Versus Medical Therapy

Lotfi Hacein-Bey, MD

A 77 y.o. healthy female patient had just walked two miles and was about to cook breakfast when she noticed the acute onset of blurred vision with vertical diplopia. Although she went to lay down, she experienced a second episode of vertical diplopia, which lasted 20 minutes and was followed by occipital headaches and walking difficulties. The same symptoms recurred the following day, followed by nausea, prompting the patient to go to her local hospital's emergency room. A CT of the head was unremarkable. MRI and MRA revealed a stenosis of the proximal basilar artery from an eccentric plaque (Figure 1) with no evidence of acute ischemic lesion. She was put on aspirin, clopidogrel and simvastatin, and referred for a neuro-interventional evaluation.

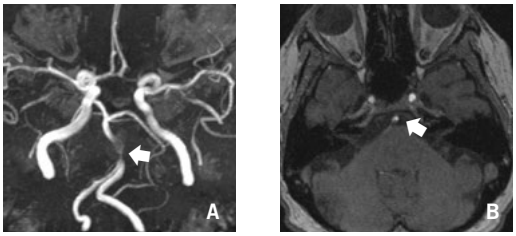

Figure 1.
MRA of the brain, collapsed view (1A) shows proximal basilar artery stenosis (arrow) with significant signal drop-out distal to the stenosis suggesting a hemodynamic effect. Axial view at the level of the stenosis shows a large eccentric plaque (arrowhead) within the basilar artery lumen.

An angiogram was obtained (Figure 2), which confirmed a stenosis of the proximal basilar artery, suggesting a likely hemodynamic mechanism for the patient's symptoms. The results of the Stenting and Aggressive Medical Management for the Prevention of Recurrent Ischemic Stroke (SAMMPRIS) trial were discussed in detail with the patient and her family. The patient was instructed to report any new symptoms.

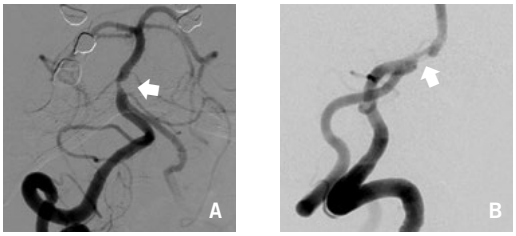

Figure 2.
Cerebral angiogram confirms a 65-70% basilar artery stenosis (arrowheads) seen on antero-posterior (2A) and lateral views (2B).

Over the following few weeks, the patient had several more TIAs, which became crescendo in nature. Fortunately, the patient did not experience a stroke. As there was clear evidence of failed medical therapy, the patient was treated with intracranial stenting of the basilar artery (Figure 3). The procedure was successful and uneventful. More importantly, there was no recurrence of symptoms at a follow-up of four months.

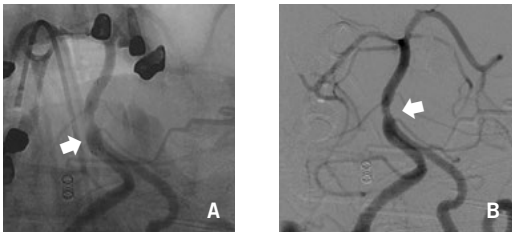

Figure 3.
Following reconstruction of the basilar artery, the stent's proximal and distal markers (arrows) are clearly seen on an unsubtracted view (3A); the reconstructed basilar artery lumen is seen on a subtracted view (3B; arrowhead).

Angioplasty and stenting of intracranial arteries has been shown to be a valid option in symptomatic patients with intracranial arterial stenotic disease, which constitute about 10% of all stroke patients. The Stenting and Aggressive Medical Management for the Prevention of Recurrent Ischemic Stroke (SAMMPRIS) trial was terminated early, with 451 patients randomized (planned 764) to either angioplasty and stenting or medical therapy, because of a higher than expected 30-day rate of stroke or death after stenting relative to medical therapy. Within 30 days of randomization, 14.7% of patients randomized to stenting suffered a stroke compared with 5.8% in the medical arm. The higher than expected rate of stroke after stenting in SAMMPRIS has raised a number of important questions as to patient selection, previous experience and training of operators with the Wingspan stent, training background and the metrics chosen for the credentialing process, some which remain unanswered.

The negative results of the SAMMPRIS trial have introduced a challenge in making treatment decisions in patients at high risk of stroke despite aggressive medical therapy. Consequently, there is a current hold on decision making, which creates an unnecessary aggravating factor in these patients, in addition to the procedural risks. Although it is likely that subgroups of patients such as those with evidence of hemodynamic failure or those with aggressive intracranial plaques will be enrolled in future trials, symptomatic patients who are currently seen require thorough monitoring, and, if there is clear evidence of failure of maximum medical therapy, treatment should be offered.

For references, comments or questions, please email Dr. Hacein-Bey at MercyNeuro@DignityHealth.org. ■

Brainwaves: Updates from Dignity Health Neurological Institute

New Neuro ICU Fills Need for Comprehensive Neuro Critical Care

The McCauley Neuro Intensive Care Unit at Mercy San Juan Medical Center is open and has filled an important need for comprehensive neurocritical care in our community. The McCauley Neuro ICU opened in mid-2013 and is a critical piece in Dignity Health Neurological Institute's work toward becoming a JCAHO-certified comprehensive stroke center. The 20-bed unit is the only Neuro ICU in the Sacramento region with board-certified neuro-intensivists available 24 hours a day, seven days a week.

The McCauley Neuro ICU has seen a steady patient volume, treating the most critically ill of neuro patients, including post-surgery and post-interventional patients as well as those diagnosed with critical conditions like subarachnoid hemorrhages and other intracranial bleeds. The unit receives a high volume of transfer patients from throughout the region. It is filling such a crucial need that a six-bed Neuro ICU will soon be available at Mercy General Hospital and a third board certified neuro-intensivist will be added to the team this summer.

Director Named for Mercy MS Achievement Center

Brian Hutchinson has been hired by Dignity Health Neurological Institute to be the first Director of the new Mercy MS Achievement Center. The Achievement Center is an adult day program which will provide much needed wellness, emotional and social support for those with advanced disability due to multiple sclerosis. The Achievement Center has been made possible by a large grant from the Conrad N. Hilton Foundation.

Brian is a physical therapist and multiple sclerosis certified specialist and is nationally recognized for his more than 20 years of experience in multiple sclerosis rehabilitation. He has served on the staff of the Rocky Mountain MS Center and was chief executive officer of the Heuga Center for MS. He has been a leader in the National MS Society and has served as president of the Consortium of Multiple Sclerosis Centers. He is widely published, has presented extensively at major meetings and has served on the editorial board of two MS journals. Most recently, Brian was a medical science liaison for Acorda Therapeutics. Brian, his wife and two daughters have relocated to Sacramento from Colorado.

The Mercy MS Achievement Center is the first of its kind in Northern California and one of fewer than a dozen centers of this scale in the U.S. The Achievement Center will operate in close partnership with other MS service providers, including the National Multiple Sclerosis Society, which since 2009 has recognized the Mercy MS Center as a Partner in Comprehensive Care.

Physicians Join Woodland Healthcare

Arish Eduljee, MD, has joined Woodland Healthcare as a neurologist at Woodland Healthcare's Cancer and Neuroscience Center. Dr. Eduljee received his doctor of medicine from Government Medical College in Surat, Gujarat, India and completed his residency in neurology at Jackson Memorial Hospital at the University of Miami, Miami Florida. Dr. Edjulee completed a fellowship in neurophysiology at UC Davis Medical Center. Dr. Eduljee's focus will be general neurology and neurophysiology.

Dennis Meredith, MD, has joined Woodland Healthcare as a spinal surgeon. Dr. Meredith received his undergraduate degree from Stanford University and his medical degree from Harvard Medical School. After completing a general surgery internship at New York Presbyterian Hospital, Dr. Meredith completed his orthopedic surgery residency at Cornell University. Dr. Meredith is skilled in managing common degenerative spinal problems as well as more complex spinal deformity, infection or malignancy. ■

Pursuit of Knowledge

Current Research Trials Available Through Dignity Health Neurological Institute

Research is an important component of a neurological institute. Providing treatment and therapy options to patients where there may not be a treatment or possible improved treatments is one of the goals at the Dignity Health Neurological Institute. Dignity Health first became involved with research in 1991 when it was a site for the original trial using intravenous t-PA in acute ischemic stroke. Since that time, Dignity Health has participated in 48 different clinical research trials. Patients are currently being enrolled into both outpatient and inpatient research trials, Mercy General Hospital and Mercy San Juan Medical Center being the two sites for inpatient trials. This article provides an overview of those studies that are currently open for enrollment.

INPATIENT

Acute Ischemic Stroke: Swift-Prime

This randomized study will assess outcomes of ischemic stroke patients receiving intravenous t-PA alone to those receiving intravenous t-PA combined with mechanical thrombectomy using Solitaire, a currently used clot retrieval device. Principal Investigator: Lucian Maidan, MD.

Acute Ischemic Stroke: POINT

NIH sponsored, randomized, double-blind study to evaluate the effectiveness of aspirin+clopidogrel in patients with minor ischemic stroke and high risk TIA over 90 days. Patients arriving to the ED within 12 hours of their onset of symptoms will be evaluated for enrollment. All patients will receive aspirin, the dose to be determined by the physician (50-325mg/day) and patients in the combined therapy arm will receive a loading dose of 600mg clopidogrel/placebo followed by a daily dose of 75mg. Principal Investigator: Lucian Maidan, MD.

Neurointerventional Radiology

Acute Ischemic Stroke: Separator 3D

Randomized study assessing the safety and effectiveness of a new device in the revascularization of large vessel occlusions in acute ischemic stroke. This device is deployed during a cerebral angiogram and is designed to break up the clot which can then be retrieved into a reperfusion catheter. Principal Investigator: George Luh, MD.

Aneurysm Treatment: LVIS

Study assessing the safety and effectiveness of using a stent to assist in the endovascular coiling of wide-neck, intracranial aneurysms. The design of this stent is thought to allow for increased flexibility, conformability and uniform neck-bridging as compared to current available devices. George Luh, MD, neurointerventional radiologist, was the first in the nation to perform implantation with this device. Dignity Health Neurological Institute continues to be one of the top enrollers in the nation. Principal Investigator: George Luh, MD.

Aneurysm Treatment: HEAT

This randomized study compares the effectiveness of a new generation Hydrogel coated coils versus the bare platinum coils in the endovascular treatment of aneurysms. Hydrogel coils are coated with a biosynthetic polymer that expands in body fluid. The hypothesis is that they will provide the highest degree of occlusion and packing density of the aneurysm leading to increased protection against recanalization and need for re-treatment. Dignity Health Neurological Institute is currently one of the top ten enrollers in the nation out of 30 active sites. Principal Investigator: George Luh, MD.

OUTPATIENT

Multiple Sclerosis: Stratify-2

A four-year follow-up study assessing the sero prevalence of JCV antibody in the relapsing multiple sclerosis population receiving or considering treatment with Tysabri. The JC virus is responsible for causing progressive multifocal leukoencephalopathy (PML) in some patients. This study hopes to stratify patients into lower or higher risk of developing PML based upon antibody status. 91 patients have been enrolled and are currently in the follow-up phase. Principal Investigator: John Schafer, MD.

Multiple Sclerosis: OPERA Trail

Randomized, double-blind study to evaluate the efficacy and safety of Ocrelizumab, a monoclonal antibody targeting B cells, in comparison to Interferon Beta-1a (Rebif) in patients with relapsing multiple sclerosis. Five patients have been enrolled, and we are currently in the follow-up phase. Principal Investigator: John Schafer, MD. ■

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