

Cerebrospinal Fluid Physiology: Problems and Possibilities

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The current definition of hydrocephalus in *Merriam-Webster's Collegiate Dictionary* is “an abnormal increase of the amount of cerebrospinal fluid within the cranial cavity that is accompanied by expansion of the cerebral ventricles and often increased intracranial pressure, skull enlargement, and cognitive decline.” This definition is far from perfect and does not even come close to describing the ways in which hydrocephalus interacts with our clinical findings and our research interests. Dr Harold Rekate¹ has attempted to give a more appropriate definition of hydrocephalus, with the goal of reaching a consensus in the neurosurgery community. Dr Rekate's proposal is shown in Figure 1. He has attempted to provide both a contemporary definition and a research definition that fit with his proposed classification scheme for hydrocephalus.

Although hydrocephalus interfaces with almost all of the subspecialty areas of neurosurgery, our understanding of the physiology of the cerebrospinal fluid (CSF) is actually quite poor. Here, I examine some of the problems associated with our understanding of CSF physiology as it relates to our understanding and treatment of hydrocephalus.

A BRIEF HISTORY

Hydrocephalus has been recognized as a medical condition for centuries. Hippocrates described it in approximately 400 BC; Galen described it in the second century, and Magendie, Key, Retzius, and Luschka furthered the study of hydrocephalus and CSF during the 19th century. Walter Dandy was fascinated by hydrocephalus. He had multiple publications regarding this common condition and attempted some innovative treatments in an effort to control it.²⁻⁴ Hydrocephalus continued to be a difficult problem for neurosurgeons to treat until the development of the 1-way shunt valve by Nulsen and Spitz.⁵

The development of the first reliable shunt systems led to the widespread perception that hydrocephalus was a “cured problem.” They definitely revolutionized the care of patients with hydrocephalus. There is no question that shunts save lives; however, research in hydrocephalus has failed to

progress at a pace comparable to that achieved in managing other central nervous system disorders. As a result, aside from improved shunt manufacturing and design and the development of endoscopic third ventriculostomy, there have been no dramatic advances in hydrocephalus clinical care and basic research for the past 60 years. There is a pressing need for basic and clinical research into this common and complex disease. The basic injury and recovery mechanisms of hydrocephalus are not adequately understood.⁶ The disparity in the volume of research between hydrocephalus and other more common neurological conditions can be illustrated by looking at publications related to hydrocephalus and those about Alzheimer disease (Figure 2). The number of articles discussing hydrocephalus falls far short of the number of publications associated with Alzheimer disease.

MERE SURVIVAL IS NOT ENOUGH

Although shunts save the lives of patients with hydrocephalus, mere survival with hydrocephalus is not enough. Hydrocephalus may be unique in that it may provide us with a novel form of reversible neuronal and glial injury, yet it is the one neurosurgically treatable condition in which we have made very little progress over the past 60 years. Shunts are our only effective treatment for hydrocephalus at the present time, yet the long-term outcome of patients with shunts seems very similar to that of 1960. Complications occur over time, and we do not have a significant understanding of the pathophysiology that accompanies this condition. Our focus seems to be more on valve control of CSF flow and less on correction of the underlying pathophysiology. We try to control hydrocephalus, not cure it.

Shunts fail at an alarming rate. There are many treatment complications, including shunt dependency, infection or foreign body reaction, inability to regulate the drainage of CSF precisely, and development of the slit ventricle syndrome (SVS). The gold-standard study evaluating shunt survival is the Randomized Trial of Cerebrospinal Fluid Shunt Design in Pediatric Hydrocephalus.⁷ In this study, the authors compared 3 different hydrocephalus shunt valve designs and found that there was no statistical difference between them. In addition, we learned that all shunt valves overdrain over time. In my experience, most children who have shunts placed during

- Hydrocephalus is a condition characterized by a dynamic imbalance between the formation (production) **and absorption** of spinal fluid resulting in an increase in the size of the fluid cavities (ventricles) within the brain.
(Note: This definition would serve for general use of all readers.)
- Hydrocephalus is a condition characterized by a dynamic imbalance between the formation (production) **and absorption** of spinal fluid that results in an increase in the size of the fluid cavities (ventricles) within the brain and in some situations results in an increase in the size of the ventricles.
(Note: This definition is most usable for those treating or studying this condition.)

FIGURE 1. Proposed revised definitions for hydrocephalus developed by Dr Harold Rekate.¹

infancy develop very small ventricles by 1 to 2 years of age because it is the nature of shunts to drain more than a physiologic amount of CSF over time. As a result, ventricles shunted early in childhood become slitlike (Figure 3). The problem, however, is not just the shunt. When we place a shunt, we change the intracranial environment significantly. Normal CSF flow is altered, and there are changes in intracranial pulsatility and intracranial pressure dynamics.

THE SVS

I would like to use SVS as an illustration of some of the problems we see as a result of chronic shunting in hydrocephalus. Characterized by headaches of various degrees, SVS may be associated with lethargy, nausea, and vomiting in a patient with slitlike ventricles. Symptoms may be very reminiscent of shunt malfunction and may be misleading to the surgeon when evaluating a patient with a suspected shunt problem. We have previously documented

the incidence of slit ventricles in 64% of pediatric patients who had shunts placed during infancy (Figure 4).⁸

Shunt overdrainage of CSF occurs with all types of shunt valves. No shunt valve has yet been shown to eliminate chronic overdrainage of CSF. If we look at the pathophysiology of what is happening with shunt placement, we find that the majority of children who have a shunt placed for the treatment of hydrocephalus undergo this procedure before 1 year of age.⁷ As a result, we are placing shunts in infants and overdraining CSF at the same time that they have their most rapid brain growth. The result is a child who has a fixed skull filled with brain parenchyma, blood, meninges, and vasculature with only small amounts of remaining CSF. There is a natural loss of intracranial compensatory mechanisms.

I believe that SVS is a phenomenon occurring only in children. Adults do not get SVS. That is not to say that adults cannot get small ventricles, because they can. They certainly may have symptoms of overdrainage and low-pressure headaches, but the pathophysiology of a full-sized brain in

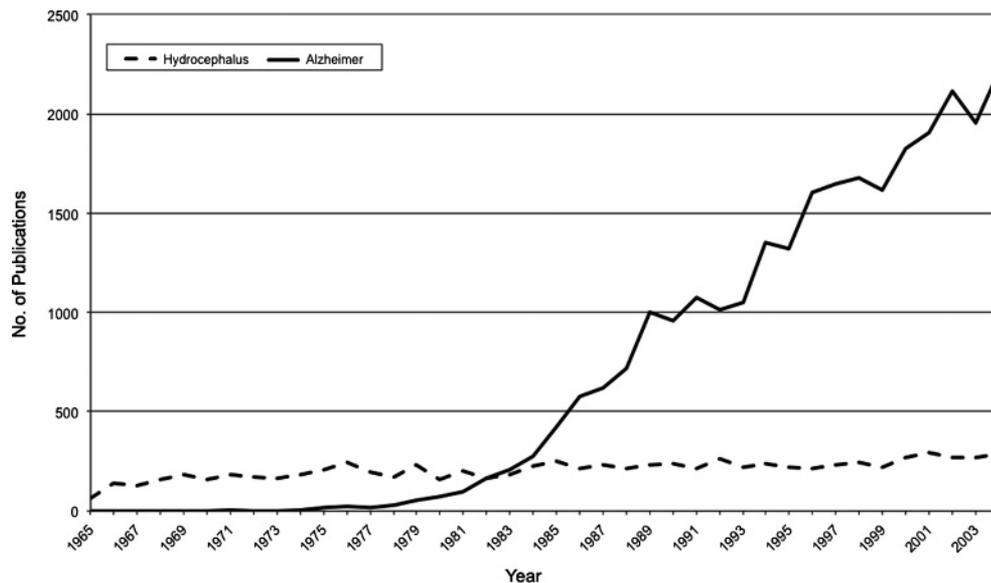


FIGURE 2. Line graph showing the number of publications listed in PubMed with MeSH major topics of "hydrocephalus" and "Alzheimer disease" between 1965 and 2004 (PubMed searched September 26, 2005). Reproduced with permission from Dr Michael Williams.



FIGURE 3. Noncontrast brain computed tomography scan showing slitlike ventricles in a patient with a ventriculoperitoneal shunt. Shunt placement occurred when the patient was 2 weeks old.

a small skull and slitlike ventricles with chronic overdrainage is unique to children whose shunts are placed during infancy. If we look at a typical occipital-frontal circumference growth chart of a patient with a shunt placed in infancy, we often see the occipital-frontal circumference becoming lower on the percentile curves as the child ages. This is a reflection of the chronic overdrainage of shunts and is part of the clinical picture that we see with these patients (Figure 5).

PATHOPHYSIOLOGY OF HYDROCEPHALUS

Our understanding of the pathophysiology of hydrocephalus is inadequate and, in some instances, may be incorrect. The traditional teaching regarding hydrocephalus does not match our clinical observation very well. Where, for example, is the physiological obstruction to flow in communicating hydrocephalus? We are taught that the arachnoid villi are the primary site of CSF absorption. This may be true only for normal CSF physiology, and even then they may not be the site of absorption of the majority of CSF

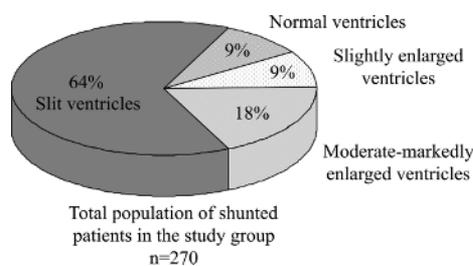


FIGURE 4. Pie graph showing the incidence of slit ventricles in a population of patients whose shunts were placed during infancy.

fluid. If the obstruction in communicating hydrocephalus was at the site of the arachnoid villi, we should see an increase in CSF along the region of the sagittal sinus. In hydrocephalus, there is increasing evidence that CSF is absorbed via the lymphatic channels; the blood vessels, especially veins and dural sinuses; and intraparenchymal water transport and absorption.⁹⁻¹⁴

Can the redistribution of CSF pulsations cause hydrocephalus? We know that in normal circumstances a significant pulse pressure is generated as the carotid artery enters the cranium. There is a natural dissipation of the energy of the carotid pulse into the subarachnoid space at the base of the brain. The subarachnoid space is a naturally occurring fluid sink. Normally, there is a significant dampening of the pulsatility between the carotid artery and the capillaries of the brain parenchyma. This dampening occurs from the process that has been called the windkessel effect¹⁵ or, more recently, the notch.^{16,17} When the subarachnoid space is eliminated at the skull base, as it usually is in communicating hydrocephalus, the carotid pulse pressure is transmitted directly into the intracranial space through the intracranial arteries. There is no “dampening” of the pulse, and there is a significant and abnormal transmission of pulsatile energy into the intracranial space.

Abnormal pulsatility associated with hydrocephalus is not a new concept. In 1962, Bering and Sato¹⁸ performed a very interesting experiment in which they excised the choroid plexus from 1 ventricle in a dog and created hydrocephalus. They found that only the ventricle with the normal choroid plexus would dilate. Wilson and Bertran¹⁹ expanded on this experiment when they clipped the choroidal artery as it led into the choroid plexus and created hydrocephalus in their animal. They found that only the ventricle with the normal pulsations from the choroidal artery would dilate. Di Rocco et al²⁰ studied this further by inserting a balloon, gated to the cardiac pulse, into the lateral ventricle of a sheep. They found they could create ventricular dilatation by pulsating the balloon and did not need to create an obstruction to create hydrocephalus.

We know that there is a hyperdynamic flow of CSF and that the flow is arterial in nature at the level of the cerebral aqueduct. We know that bulk CSF flow accounts for approximately 0.3 cm³/min at the level of the aqueduct but the pulsatile flow is 2 cm³/min. Pulsatile flow is slower in the aqueduct and faster in the basilar cisterns and craniocervical junction, yet there continues to be a slower bulk flow over the cerebral hemispheres.¹⁷

Hydrocephalus is associated with marked abnormalities of CSF flow and is associated with increased aqueductal pulsatility. Wagshul et al¹⁷ have shown that aqueductal stroke volume may predict the severity of hydrocephalus. We have good reason to suspect that there is a redistribution of pulsatility in hydrocephalus. How does this redistribution

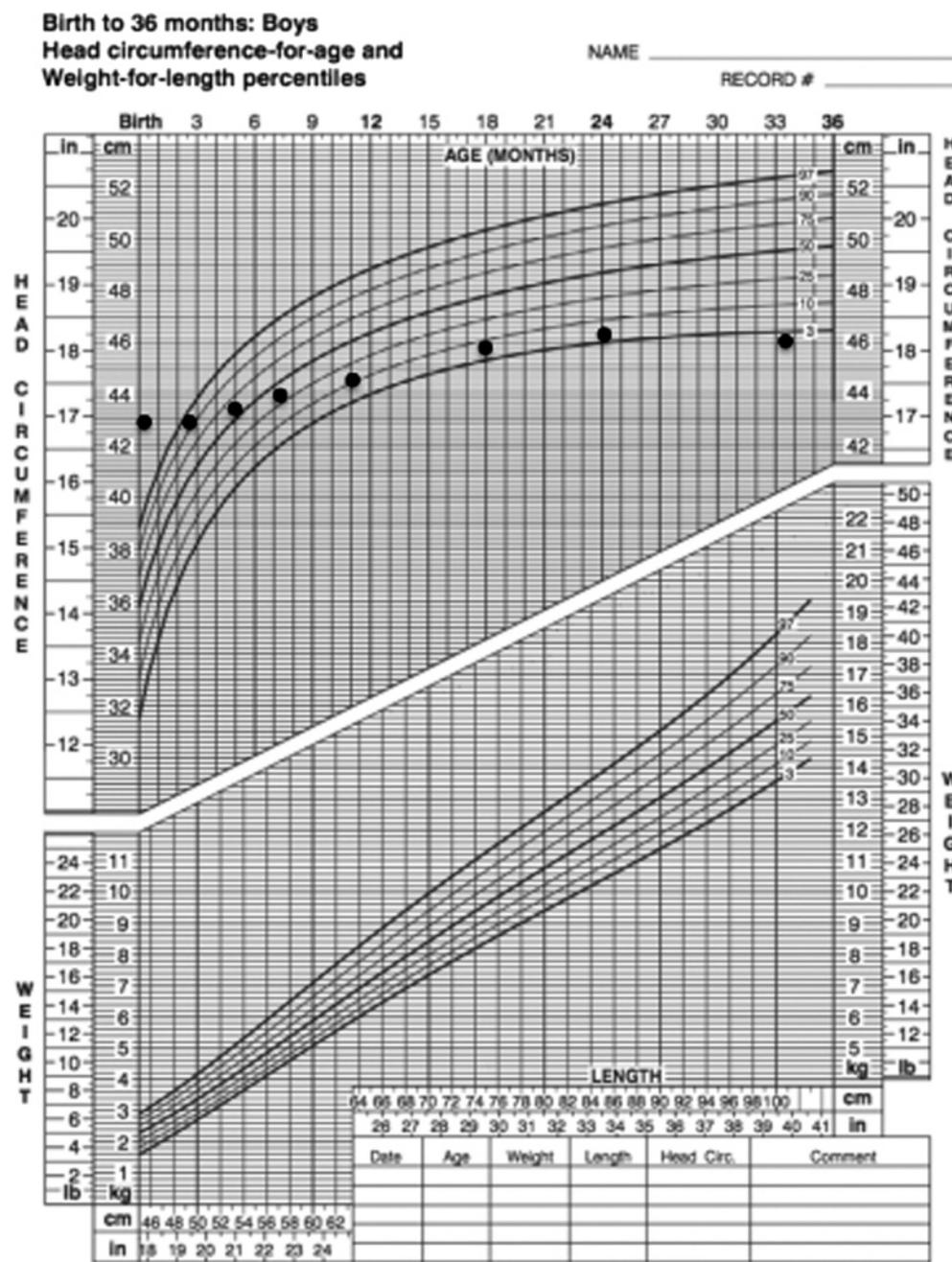


FIGURE 5. A normal male head growth chart showing a decline in the percentile size of the occipital-frontal circumference as the patient grows from birth to 3 years of age. This is typical of patients who have experienced chronic shunt overdrainage when shunted in infancy.

occur? How does the transfer function account for the processing of the arterial pulse as it enters the cranium? Madsen and colleagues¹⁶ have described the phase, amplitude, and the notch function of the transfer between arterial blood pressure and cranial blood pressure. They noted the disappearance and the reappearance of the notch with changes

in intracranial pressures. Foltz et al²¹ documented that the amplitude of the intracranial pulse pressure increases with increasing intracranial pressure; however, they also noted that the amplitude of the intracranial pulse pressure increases with decreasing intracranial pressure. Most recently, experiments by Wagshul et al²² using a state-of-the-art technique to

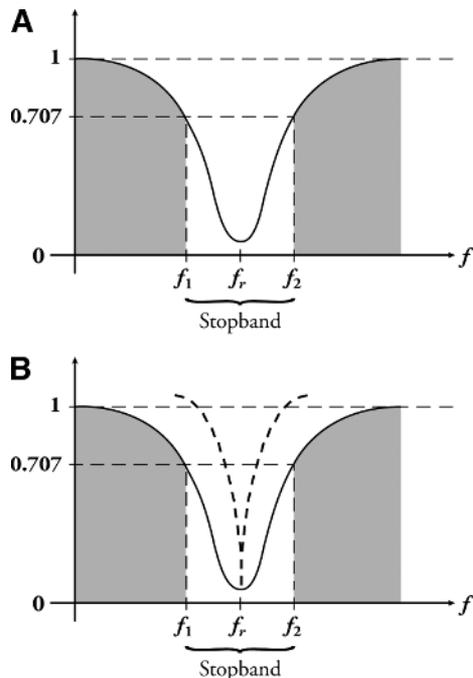


FIGURE 6. A, a typical-appearing stop band. B, a stop band suggesting that the “notch” has become much more narrow, thereby making it more difficult to locate.

visualize and quantify capillary pulsatility in living animals have suggested that the pulsatility index does in fact change during acute and chronic phases of communicating hydrocephalus. Studies such as these should be continued because they will help reveal the true mechanism of pulsatility changes in hydrocephalus.

How does all of this relate to SVS? Let me illustrate with a case. A 15-year-old boy who had had a shunt placed during infancy had no prior shunt malfunctions and was doing well in school. He presented with a 2-day history of progressive headaches. A computed tomography scan showed slight enlargement of his ventricles compared with his prior studies, and he underwent a shunt revision. One year later, he had had 5 shunt revisions and 1 shunt infection, his school performance had declined, and he was depressed. So, how does this relate to SVS? The notch, or the climate in the intracranial environment at which the patient is most comfortable, can be compared with a stop band (Figure 6A). A stop band might be considered similar to tuning to a single radio station when there are many stations on the dial. What happens in SVS when we have changed intracranial pulsatility for many years in a given patient? Has that notch moved to the left so that it is in a different place? Has it moved to the right? Has the notch been eliminated? I do not think we know the answer, but I have a strong suspicion that the notch has become very narrow (Figure 6B). When a patient has a change in his or her intracranial environment such as a shunt revision,

after having adjusted to the abnormal environment created by chronic shunting, it is often difficult to find the notch again after shunt revision. As a result, it is hard for us to create the same intracranial environment at which the patient was comfortable. This is really a nightmare. This patient has done so well for so long, and now we cannot seem to “get it right.” We cannot hit the notch, that place where the patient was so comfortable for so long. We need a better understanding of this phenomenon.

THE HYDROCEPHALUS CLINICAL RESEARCH NETWORK

I want to talk about one of the bright spots as we look to the future in our management of hydrocephalus. The Hydrocephalus Clinical Research Network (HCRN) was the vision of Dr John Kestle. His colleagues and he have created the HCRN to study hydrocephalus and shunts in a clinical setting. The old model for studying shunts and hydrocephalus was based on studies done at independent centers with an interest in hydrocephalus. But the accrual rate was slow, even with the high volume of patients with hydrocephalus. It was hard to justify full-time research personnel at given centers. Data collection became the responsibility of the surgeon, and funding was limited to a specific trial. The result of this was delayed acquisition of data and missing data.

With the development of the HCRN, multiple projects are underway simultaneously at multiple centers. There are investigators and coordinators in each center. These are all high-volume centers, with clinical research expertise, a history of cooperation in clinical trials, and pediatric neurosurgical expertise. The HCRN Data Coordinating Center is in Salt Lake City at the University of Utah. There are 7 clinical sites, each with an HCRN investigator and a clinical coordinator: Salt Lake City, Toronto, Birmingham, Houston, Seattle, Pittsburgh, and St Louis. This ensures that a large study population can be accrued across the whole network. The HCRN protocols to date have included a quality improvement protocol to reduce shunt infection, a protocol for management of intraventricular hemorrhage, and an ultrasound-guided shunt placement protocol. In addition, there is a registry for shunt surgery, endoscopy third ventriculostomy, and shunt infection.

The shunt infection protocol is shown in Figure 7. It was quite an accomplishment to get 7 centers to perform shunt surgery exactly the same way in every case, including all of the surgeons in each of the 7 centers. As a result, however, the centers in the network have gone from a preprotocol infection rate of 8.8% to a postprotocol infection rate of 5.7% (unpublished date, Kestle et al). Surgeons who have performed ≥ 50 procedures have an infection rate of 4.2% when they have perfect compliance with the protocol. If there is 1 violation of the protocol, the infection rate rises to 5.1%;

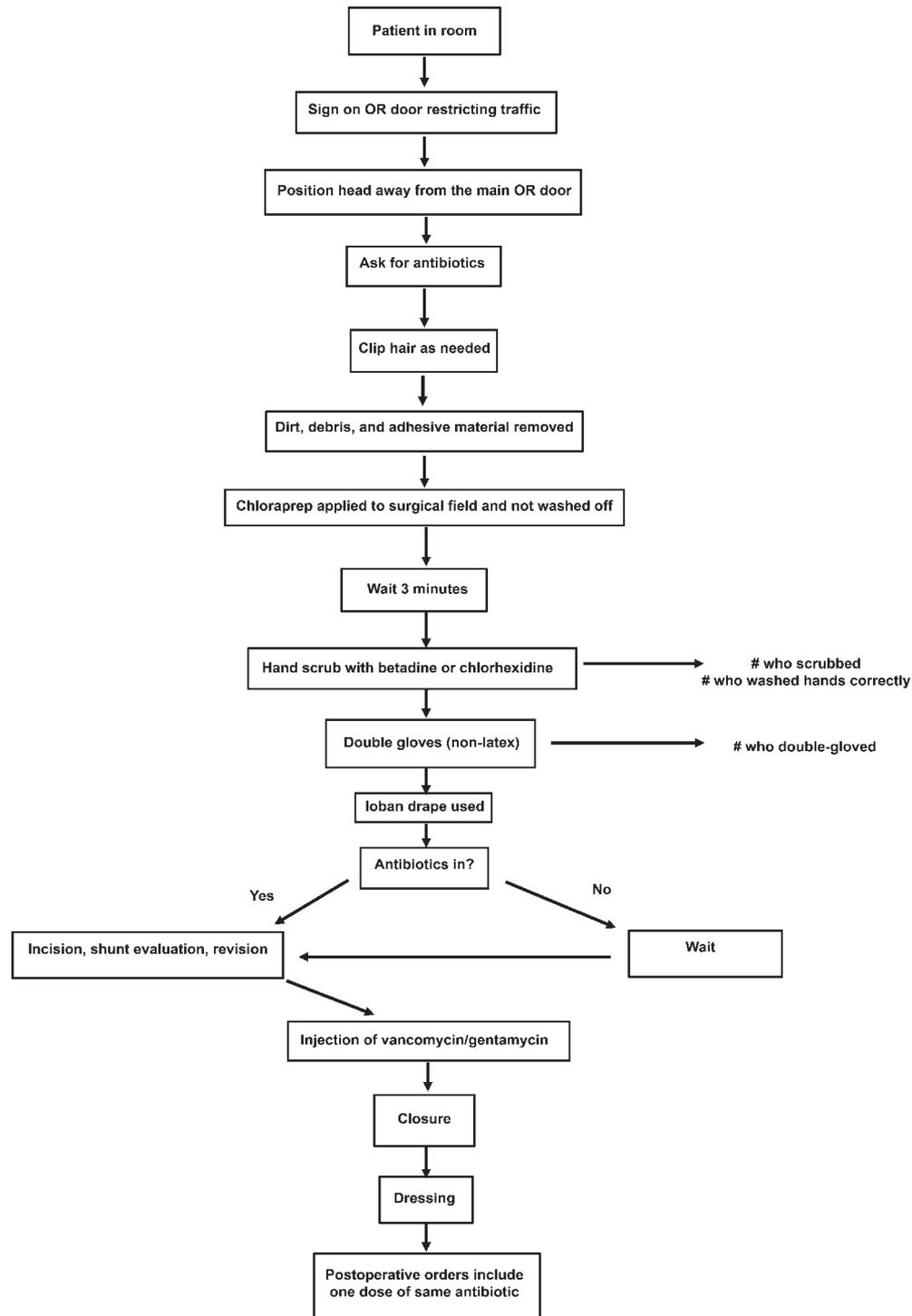


FIGURE 7. The Hydrocephalus Clinical Research Network protocol for shunt surgery. Reproduced with permission from Kestle et al.

with 2 violations, it is 13.3%. The procedure infection rates throughout the network are 7.0% for insertion, 4.2% for revisions, 9.0% for insertion after an external ventricular drain, and 11.1% for insertion after infection.

The Hydrocephalus Registry began enrollment in 2008; a total of 1545 patients had been registered as of September 2010. Overall, 2670 procedures have been performed and 450 data points per event have been collected. The registry is based

on the Children's Oncology Group model. There is a Web-based, deidentified database. The HCRN was recently awarded \$994 700 from the US National Institutes of Health (grant 1RC1NS068943-01) to continue development of the network and to provide structural support. The HCRN and similar clinical trials have the potential to change and improve our management of patients with hydrocephalus.

CONCLUSION

Hydrocephalus remains a significant challenge that interfaces with almost all that we do in neurosurgery (congenital, aging, trauma, tumors, vascular, infection, etc). Thus far, no specific treatment or shunt type has been shown to be the best option. Shunt overdrainage is common in patients with shunts, and in childhood, the development of SVS may have a significant impact on outcome. A focus on the underlying pathophysiology of hydrocephalus, including CSF pulsatility, bulk flow, absorption, ependymal abnormalities, and genetic causes, may pay long-term benefits. Large-scale clinical trials show promise of improvement in long-term outcome and more effective treatments for patients with hydrocephalus.

Disclosure

The author has no personal financial or institutional interests in any of the drugs, materials, or devices described in this article.

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