The CURE Algorithm and Clinical Protocol for Infant Hydrocephalus

Introduction:

Hydrocephalus is a neurological condition characterized by ventriculomegaly and abnormal head growth, which if left untreated can cause significant disability and developmental delay.[1] The most recent estimates suggest that there are greater than 400,000 new cases each year with the vast majority occurring in low-and-middle income countries.[2] Appropriate diagnosis and operative selection are equally important to technical skill in management of hydrocephalus. The clinical indications for treatment described in this protocol provide a framework that can assist the neurosurgeon to decide when surgical intervention is appropriate.

1. Diagnosis and Decision to Treat

The primary screening method and diagnostic tool used for evaluation of hydrocephalus is head growth over time. It is important to note that having an enlarged head alone does not automatically entail a diagnosis of hydrocephalus. There are several causes of an enlarged head, such as "benign macrocephaly," which are not hydrocephalus and do not require surgical intervention. Additionally, hydrocephalus early in life can occasionally resolve itself. It should also be noted that when the anterior fontanel (soft spot) is depressed this suggests that treatment is not necessary, even if the head is enlarged. It is of primary importance that every child being evaluated for hydrocephalus have their head circumference measured and plotted on a World Health Organization (WHO) growth chart (Figure 1) at every visit to determine percentile and track growth over time.
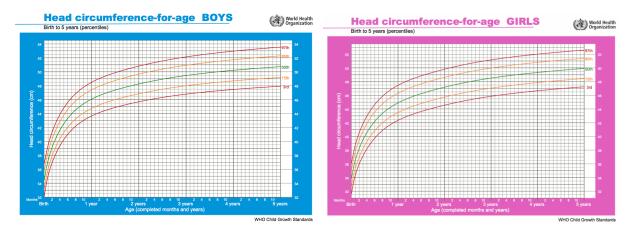

Figure 1: WHO Head Circumference Charts for boys and girls from birth to 5 years of age. Available at https://www.who.int/childgrowth/standards/en/.

In order to qualify for treatment, the infant should have more than one of the following features:

    a) Head circumference percentile that is increasing faster than normal, skipping
        percentile curves on the growth chart over time.
    b) The anterior fontanel is bulging or full while the child is quiet and held upright
    c) There is forced downward gaze of the eyes ("sunset sign") or the eyes are
    crossed d) the scalp veins are distended
    e) There is abnormal irritability, lethargy, poor feeding, or vomiting
    f) In the child with spina bifida, noisy breathing (stridor), apnea spells, or regurgitation
        of feeds through the nose can be ominous signs of brain stem dysfunction
        because of the Chiari malformation, and can signal the need to treat
        hydrocephalus
    g) A head ultrasound or other cranial imaging that shows definite enlargement of the
    ventricles

The presence of any of these signs alone, does always not mean that hydrocephalus is present. In certain cases, there can be stable enlargement of the ventricles in a child who has no symptoms and it may take time to determine whether this is progressive and requires treatment. Asking the patient to return in approximately one month for a second head circumference measurement and repeat imaging carries minimal risk and might prevent an unnecessary operation. For instance, if ventricles appear stable with normal increase in size relative to head growth, stable Frontal Occipital Horn Ratio (FOHR - See Below), and normal head growth along the same percentile curve then no operation is indicated.

It is important to note that an infant may have several of the above symptoms, but if the head ultrasound is normal, the problem is something other than hydrocephalus. In addition, if the ventricles are larger than normal but there are none of the above described clinical signs, one should not do an operation without proving that the ventricles are definitely enlarging abnormally over time.

In limited resource settings in which many patients need treatment it may be necessary to triage patients so that early treatment goes to those who need it the most. Treating hydrocephalus is typically not an emergency in the young infant because the skull is not fused and can expand to accommodate the extra fluid and avoid dangerously raised pressures. However, the earlier that hydrocephalus is treated in the young infant whose brain is growing rapidly, the better will be the developmental outcome. The majority of normal brain growth occurs in the first two years of life.[3] Younger infants just recently diagnosed should take priority over older children with very large heads because in the older children the majority of brain growth has already been missed and the damage has been done. For young infants diagnosed before the head size has enlarged dramatically, there is hope of intervening before there is irreversible damage to the brain. When one is confronted with a large backlog of cases, triage is essential to select the youngest infants for treatment first. Of course, the child who is acutely ill from hydrocephalus is an emergency and prompt treatment is required to save life. Such children can be recognized by lethargy, vomiting, and a tense fontanel.

One must be very cautious in treating a child older than the age of 2 years with a very large head unless he or she is clearly ill from hydrocephalus (elevated intracranial pressure). There are many older children who have survived the initial hydrocephalus and have disabilities as a result (such as developmental delay or visual impairment), but in whom the process has arrested itself and treatment will not help, but only risk harming, the child.

Infants with no brain but only fluid in the intracranial space (hydranenephaly) have a terrible prognosis. These children cannot develop and, despite treatment of the hydrocephalus, will usually die within several years. Treating hydrocephalus in these infants should be considered but is only for palliation when the head is continuing to enlarge, and the infant appears to be suffering. Due to the prenatal injury in these cases, there can be no meaningful development beyond the brain stem reflexes that make up the majority of normal newborn behaviors (sucking, crying, movement, etc). If treatment is undertaken, the parents must be made to understand that this will not help the child develop and that he or she will have very minimal function for the duration of their short life.

2. Determining the cause of hydrocephalus

In low-resource countries, there may be a very high incidence of hydrocephalus that develops from neonatal infection – post-infectious hydrocephalus (PIH).[4] Below are some clues that can be helpful in assigning a possible cause for the hydrocephalus.

a) Sometimes PIH may prove to be the cause even if there is not a clear history of a previous febrile illness.[5]
b) Distorted brain anatomy or areas of cyst formation in the brain in addition to the enlarged ventricles is typical of PIH.
c) If the lateral and third ventricles are enlarged and the 4th ventricle is small or normal in size, this is a good indication that the aqueduct is blocked. This can be congenital aqueductal stenosis. But the aqueduct is often obstructed by pus or scar in children with PIH as well.[6]
d) Hydrocephalus develops in more than half of infants with myelomeningocele (open spina bifida) because of the abnormal brain anatomy (Chiari malformation). It is important to note that most infants with spina bifida have enlarged ventricles
even if they do not have progressive hydrocephalus. As noted in section 1 above, stable enlarged ventricles alone does not mean that there is hydrocephalus.[7]
e) The presence of a large posterior fossa fluid collection around the cerebellum that communicates with the 4th ventricle can be an indication that the child has an abnormality in the category of the Dandy-Walker complex.[8]
f) Sometimes there is no identifiable cause of hydrocephalus on the ultrasound which is often described as "Congenital Idiopathic Hydrocephalus."[6]

3. Treatment selection algorithm

Figure 2 is an algorithm, or decision tree, that is based upon more than a decade of clinical research at CURE Children's Hospital of Uganda.[4,7,9,10] It is designed to help guide the decision-making process of whether to do ETV/CPC or place a shunt with the goal of minimizing risk and maximizing treatment success. This algorithm, of course, does not apply to treatment sites that do not have the option of ETV/CPC.

The CURE Protocol, therefore, emphasizes a primary attempt at endoscopic treatment, unless the preoperative imaging suggests this is not technically feasible. No patients should undergo intervention for hydrocephalus without first undergoing cranial imaging – either computed tomography or cranial ultrasound. Findings at the time of endoscopy then dictate when ETV should be supplemented with CPC or abandoned in favor of shunt, according to the evidence-based algorithm. For example, if there is a diagnosis of post-infectious hydrocephalus and obstruction of the aqueduct of Sylvius is observed at endoscopy, then ETV alone is performed without CPC.[11] As well, if, after completing the ETV, scarring of the prepontine cistern is discovered, then a shunt is placed under the same anesthesia because the chance of ETV or ETV/CPC success is low in those patients.[10] If the original imaging shows such anatomic distortion due to infectious loculations, intraventricular scarring, or other congenital causes, such that endoscopic access to the floor of the third ventricle appears untenable or unsafe, a shunt is primarily placed, although this may be in concert with endoscopic fenestration of ventricular loculations, if necessary.
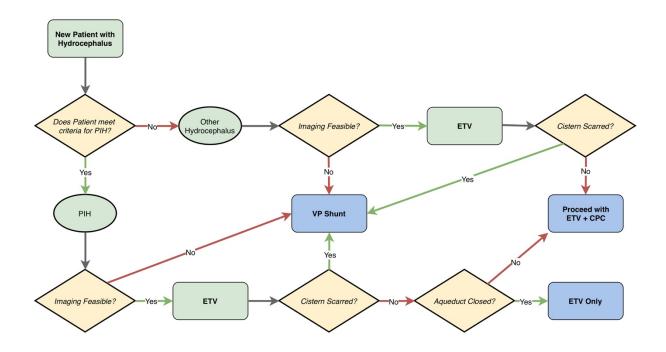

Figure 2: The CURE Algorithm for initial management of pediatric hydrocephalus. PIH = Post-infectious Hydrocephalus; VP Shunt = Ventriculoperitoneal Shunt; ETV = Endoscopic Third Ventriculostomy; CPC = Choroid Plexus Cauterization.

4. Post-Operative Care

We recommend the child remain in hospital for at least 2 days after the operation for clinical observation. There is no proof that giving antibiotics after surgery is of any benefit, and we do not recommend it. However, a preoperative dose of IV antibiotics in the operating room just prior to the incision is of benefit and should be given.[12] If the child comes from a great distance and would not be able to return in case of complications, then a longer time of observation is in order. Also, if the success of the treatment is in question, the child should not be discharged. If the shunt is working or if the ETV/CPC is likely to be a success, the
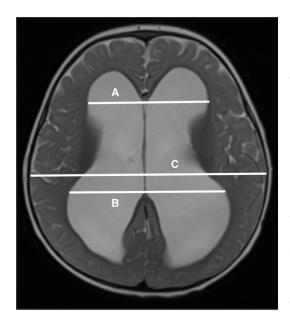
fontanel should be flat and soft. Also, it is not uncommon for infants to have some vomiting and poor feeding, as well as low grade fever, in the first 2-3 days following surgery. One should ensure that these have resolved prior to discharge.

5. Follow up

These children need their closest follow up in the first 6 months. For shunts, the majority of operative infections occur within 90 days. And, for both ETV/CPC and shunts, the likelihood of failure is highest during this period.[9] The great majority of ETV/CPC failures will occur by 6 months. Beyond that time, treatment failure is very unusual.[13] However, for shunts, failure can occur at any time later during the patient's life. Our recommendation is to see the infant in follow up at about 1 month, 3 months, and 6 months after surgery and then once per year thereafter if this is possible. For children who have been doing well after ETV/CPC for more than two years, however, it is less important to continue seeing them after that time.

At the time of clinical follow up, in addition to the child's general condition and development, the key things to check are:

a) The head circumference (plotted on the child's growth curve that is kept in his or her medical record)
b) The condition of the fontanel, which should be flat and soft
c) The size of the ventricles on the cranial ultrasound or CT imaging (as determined by the Frontal Occipital Horn Ratio) which should be stable or smaller

The Frontal Occipital Horn Ratio (FOHR) can easily be measured on cranial ultrasound, CT, or MRI. Using the measurements illustrated in **Figure 3** the FOHR is calculated as: FOHR = (A + B)/(2 x C) in which A is the greatest diameter of the frontal horn, B is the greatest diameter of the occipital horn, and C is the greatest biparietal diameter measured from cortex to cortex. A normal FOHR is 0.37.[14] However, it should be noted that in the patient with pediatric hydrocephalus the actual value is less important than the trend over time. An increasing FOHR indicates that a greater proportion of their total brain volume is comprised of ventricular CSF and thus may indicate ETV failure. We recommend the regular use of FOHR in conjunction with head circumference and clinical assessment as primary methods for assessing treatment success and failure in follow-up.

Figure 3: Diagram illustrating the standard measurements necessary to calculate the Frontal-Occipital Horn Ratio. A = Greatest diameter of the frontal horn, B = Greatest diameter of the occipital horn, and C = Greatest biparietal diameter measured from cortex to cortex.

5. Identification and management of treatment failure

Treatment failure is often characterized by recurrence of the original signs and symptoms of hydrocephalus as outlined for the diagnosis of hydrocephalus in Section 1.
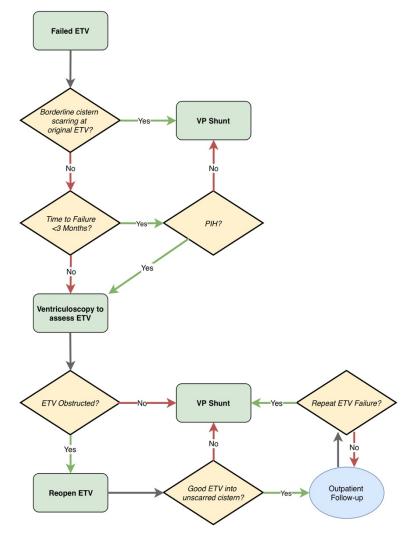

Figure 4: CURE Algorithm for evaluation of failed ETV or ETV/CPC in the setting of pediatric hydrocephalus. ETV = Endoscopic Third Ventriculostomy; VP Shunt = Ventriculoperitoneal Shunt.

ETV/CPC failure
Failure of the ETV/CPC should be considered if 1.) the child's head is growing at an abnormally rapid rate (increasing percentiles for age over time), 2.) the fontanel is full, 3.) the child develops regression of developmental milestones, 3.) the ventricles are increasing on imaging as evidenced by an increasing FOHR. If the treatment had been working initially, for instance at the 1-month follow-up, before signs of failure appeared, for instance, at the 3 month follow-up, failure might be secondary to closure of the ETV. In that case, one should consider repeat endoscopy to reopen the ETV if it is found to be obstructed. Refer to **Figure 4** for the decision tree that will help guide this decision. If the ETV/CPC has failed from the very beginning or was noted to be marginal at the time of the initial surgery then it is best to just proceed with shunt placement. Again, it is unusual for ETV/CPC to fail after 6 months. When this occurs, it is usually because of ETV closure and there is a high rate of success with simply reopening the ETV.[15]

Shunt failure
The child with a shunt who presents with signs and symptoms of acute hydrocephalus will require surgery to explore the shunt, testing its different components to determine what portion is obstructed. The most common cause of shunt malfunction is obstruction of the ventricular catheter, with poor flow of CSF found at the time of exploration. Regardless of whether the ventricular catheter needs to be changed, the distal part of the shunt should always be tested.

If a column of fluid in a manometer or a vertical length of IV tubing fails to flow easily through the valve and into the abdomen, then either the valve or the distal tubing is obstructed. At that point, the valve should be disconnected from the distal tubing and flow checked again in both components individually followed by replacement and reconnection of any obstructed portions of the shunt system.

References:

1   Warf BC, Alkire BC, Bhai S, *et al.* Costs and benefits of neurosurgical intervention for infant hydrocephalus in sub-Saharan Africa. *J Neurosurg Pediatr* 2011;**8**:509–21. doi:10.3171/2011.8.PEDS11163

2   Dewan MC, Rattani A, Mekary R, *et al.* Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis. *J Neurosurg* 2018;:1–15. doi:10.3171/2017.10.JNS17439

3   Mandell JG, Kulkarni AV, Warf BC, *et al.* Volumetric brain analysis in neurosurgery: Part 2. Brain and CSF volumes discriminate neurocognitive outcomes in hydrocephalus. *J Neurosurg Pediatr* 2015;**15**:125–32. doi:10.3171/2014.9.PEDS12427

4   Warf BC. Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy. *J Neurosurg* 2005;**102**:1–15. doi:10.3171/ped.2005.102.1.0001

5   Warf BC, Dagi AR, Kaaya BN, *et al.* Five-year survival and outcome of treatment for postinfectious hydrocephalus in Ugandan infants. *J Neurosurg Pediatr* 2011;**8**:502–8. doi:10.3171/2011.8.PEDS11221

6   Warf BC, Tracy S, Mugamba J. Long-term outcome for endoscopic third ventriculostomy alone or in combination with choroid plexus cauterization for congenital aqueductal stenosis in African infants. *J Neurosurg Pediatr* 2012;**10**:108–11. doi:10.3171/2012.4.PEDS1253

7   Warf BC, Campbell JW. Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment of hydrocephalus for infants with myelomeningocele: long-term results of a prospective intent-to-treat study in 115 East African infants. *J Neurosurg Pediatr* 2008;**2**:310–6. doi:10.3171/PED.2008.2.11.310

8   Warf BC, Dewan M, Mugamba J. Management of Dandy-Walker complex-associated infant hydrocephalus by combined endoscopic third ventriculostomy and choroid plexus cauterization. *J Neurosurg Pediatr* 2011;**8**:377–83. doi:10.3171/2011.7.PEDS1198

9   Kulkarni AV, Schiff SJ, Mbabazi-Kabachelor E, *et al.* Endoscopic Treatment versus Shunting for Infant Hydrocephalus in Uganda. *N Engl J Med* 2017;**377**:2456–64. doi:10.1056/NEJMoa1707568

10   Warf BC, Kulkarni AV. Intraoperative assessment of cerebral aqueduct patency and cisternal scarring: impact on success of endoscopic third ventriculostomy in 403 African children. *J Neurosurg Pediatr* 2010;**5**:204–9. doi:10.3171/2009.9.PEDS09304

11   Warf BC. Comparison of endoscopic third ventriculostomy alone and combined with choroid plexus cauterization in infants younger than 1 year of age: a prospective study in 550 African children. *J Neurosurg* 2005;**103**:475–81. doi:10.3171/ped.2005.103.6.0475

12   Klimo P, Van Poppel M, Thompson CJ, *et al.* Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 6: Preoperative antibiotics for shunt surgery in children with hydrocephalus: a systematic review and meta-analysis. *J Neurosurg Pediatr* 2014;**14 Suppl 1**:44–52. doi:10.3171/2014.7.PEDS14326

13 Hader WJ, Drake J, Cochrane D, *et al.* Death after late failure of third ventriculostomy in children. Report of three cases. *J Neurosurg* 2002;**97**:211–5. doi:10.3171/jns.2002.97.1.0211

14 O'Hayon BB, Drake JM, Ossip MG, *et al.* Frontal and occipital horn ratio: A linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. *Pediatr Neurosurg* 1998;**29**:245–9. doi:10.1159/000028730

15 Marano PJ, Stone SSD, Mugamba J, *et al.* Reopening of an obstructed third ventriculostomy: long-term success and factors affecting outcome in 215 infants. *J Neurosurg Pediatr* 2015;**15**:399–405. doi:10.3171/2014.10.PEDS14250