Given the difficulties intrinsic to safely maintaining shunt function in rural East Africa, we have pursued endoscopic methods for treating infant hydrocephalus with the goal of preventing shunt dependence when possible.\textsuperscript{14,15} We found that, for infants less than 1 year of age, combining CPC with ETV significantly increased the likelihood of treatment success over ETV alone, and have subsequently demonstrated the efficacy of the combined ETV-CPC procedure in treating infant hydrocephalus of a variety of etiologies.\textsuperscript{14,16,18,21,22} Nearly all endoscopic treatment failures were evident being shunt survival after failed endoscopic treatment of hydrocephalus

Clinical article

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Object. It is not known whether previous endoscopic third ventriculostomy (ETV) affects the risk of shunt failure. Different epochs of hydrocephalus treatment at the CURE Children's Hospital of Uganda (CCHU)—initially placing CSF shunts in all patients, then attempting ETV in all patients, and finally attempting ETV combined with choroid plexus cauterization (CPC) in all patients—provided the opportunity to assess whether prior endoscopic surgery affected shunt survival.

Methods. With appropriate institutional approvals, the authors reviewed the CCHU clinical database to identify 2329 patients treated for hydrocephalus from December 2000 to May 2007. Initial ventriculoperitoneal (VP) shunt placement was performed in 900 patients under one of three circumstances: 1) primary nonselective VP shunt placement with no endoscopy (255 patients); 2) VP shunt placement at the time of abandoned ETV attempt (with or without CPC) (370 patients); 3) VP shunt placement subsequent to a completed but failed ETV (with or without CPC) (275 patients). We analyzed time to shunt failure using the Kaplan-Meier method to construct survival curves, Cox proportional hazards regression modeling, and risk-adjusted analyses to account for possible confounding differences among these groups.

Results. Shunt failure occurred in 299 patients, and the mean duration of follow-up for the remaining 601 was 28.7 months (median 18.8, interquartile range 4.1–46.3). There was no significant difference in operative mortality (p = 0.07 by log-rank and p = 0.14 by Cox regression adjusted for age and hydrocephalus etiology) or shunt infection (p = 0.94, log-rank) among the 3 groups. There was no difference in shunt survival between patients treated with primary shunt placement and those who underwent shunt placement at the time of an abandoned ETV attempt (adjusted hazard ratio [HR] 1.14, 95% CI 0.86–1.51, p = 0.35).

Those who underwent shunt placement after a completed but failed ETV (with or without CPC) had a lower risk of shunt failure (p = 0.008, log-rank), with a hazard ratio (adjusted for age at shunting and etiology) of 0.72 (95% CI 0.53–0.98), p = 0.03, compared with those who underwent primary shunt placement without endoscopy; but this was observed only in patients with postinfectious hydrocephalus (PIH) (adjusted HR 0.55, 95% CI 0.36–0.85, p = 0.007), and no effect was apparent for hydrocephalus of noninfectious etiologies (adjusted HR 0.98, 95% CI 0.64–1.50, p = 0.92). Improved shunt survival after failed ETV in the PIH group may be an artifact of selection arising from the inherent heterogeneity of ventricular damage within that group, or a consequence of the timing of shunt placement. The anticipated benefit of CPC in preventing future ventricular catheter obstruction was not observed.

Conclusions. A paradigm for infant hydrocephalus involving intention to treat by ETV with or without CPC had no adverse effect on mortality or on subsequent shunt survival or infection risk. This study failed to demonstrate a positive effect of prior ETV or CPC on shunt survival.

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**Key Words**: shunt outcome • endoscopic third ventriculostomy • choroid plexus cauterization • hydrocephalus • Africa • developing countries
fore 6 months, and these patients were ultimately treated with CSF shunting.14–16,18–22

It is not known whether a previous, but failed, ETV, with or without CPC, affects the future risk of shunt failure. It has been suggested by others that an ETV performed at the time of or prior to shunt placement might decrease the subsequent risk of shunt malfunction.2,12 Since our treatment paradigm at CCHU had evolved toward first attempting endoscopic treatment in all patients, we were interested to know whether, compared with patients treated with primary shunt placement, those with failed or abandoned endoscopic treatment might have an altered incidence of shunt malfunction or infection over time. It seemed plausible that prior endoscopic treatment might decrease the risk of future shunt malfunction because, for instance, 1) a persistently patent ETV might decrease shunt dependence over time, or 2) decreased choroid plexus in the ventricle following CPC might reduce the risk of future ventricular catheter obstruction. Alternatively, however, prior endoscopic treatment might increase the risk of subsequent shunt failure for various reasons, including the following: 1) blood or suspended debris in the CSF might increase the risk of subsequent ventricular catheter or valve obstruction; 2) there could be an increased risk of shunt infection when placement follows a concomitant or recent endoscopic procedure; 3) CPC could increase the risk of shunt infection, given the potential role of choroid plexus in the inflammatory response.24

Different epochs of treatment at the CURE Children’s Hospital of Uganda (initially treating all hydrocephalus patients with shunt placement, then attempting ETV in all patients, and finally attempting ETV-CPC in all patients), without a change in the patient population or the surgeons involved, provided the opportunity to look for an effect. The retrospective study presented here was carried out to assess whether prior endoscopic surgery affected shunt survival.

Methods

After obtaining appropriate institutional approval from both Children’s Hospital Boston and CCHU, we reviewed the CCHU database containing prospectively collected clinical data on patients requiring treatment for hydrocephalus at CCHU in Mbale, Uganda, between December 2000 and May 2007. This period covers 2 distinct epochs of treatment philosophy at CCHU: primary placement of a CSF shunt without the use of endoscopy, and primarily attempting endoscopic treatment in all patients in an effort to avoid shunt placement. The present study includes an extended follow-up of some endoscopically treated patients who have been reported on in previous publications (cited below). Before June 2001, all patients with hydrocephalus were noneendoscopically treated by placement of a VP shunt. We previously reported our initial 1-year outcome for CSF shunting at CCHU, demonstrating that shunt failure and infection risks at 1 year using the inexpensive Chhabra shunt were equivalent to those using the Codman-Hakim Micro Precision Valve shunt system and that these outcomes were consistent with those reported from other series in North America.13 After June 2001, our treatment protocol changed, and nearly all patients underwent endoscopy for attempted ETV,15 and later on ETV-CPC,14 without regard for age or etiology of hydrocephalus. In some of these patients, the ETV attempt had to be abandoned for shunt placement because of difficult anatomy, poor visibility, or a severely scarred prepontine cistern discovered upon creation of the ETV. Patients with nontransparent CSF were not treated with immediate shunt placement but, rather, underwent placement of a ventricular access device for serial tapping until the CSF cleared. These patients subsequently underwent repeat endoscopy for attempted ETV or, in the case of the primary shunt treatment group, VP shunt placement. The results for the initial intention to treat by endoscopy for all patients during the same time period as the present study—including aborted ETV attempts, failed ETV (with or without CPC), and successful ETV (with or without CPC)—have been previously reported.20

Thus, all patients in this study received a VP shunt under one of the following circumstances: 1) those primarily and noneendoscopically treated with CSF shunting with no endoscopy; 2) those treated with CSF shunting after failure of successfully completed endoscopy (ETV with or without CPC); 3) those treated with CSF shunting when the ETV attempt was abandoned (with or without CPC).

Patients were predominantly from Uganda, although some were from other regions in East Africa. Of 2329 patients treated for hydrocephalus during this study period, we identified 914 in whom a VP shunt had been placed. Fourteen patients (1.5%) were eliminated from further study because they had previously undergone shunt placement elsewhere or because of incomplete information. Thus, 900 patients formed the basis of this analysis. When possible, patients lost to follow-up were contacted by telephone or home visit. The database record for every patient was reviewed independently in duplicate, including by the principle author, who was also the primary surgeon in the majority of procedures performed during this period (B.C.W.). For each patient the following information was obtained: date and nature of initial and subsequent operations, age at treatment, etiology of hydrocephalus (postinfectious, myelomeningocele, or another noninfectious cause) as defined previously,15 date of shunt failure or death, and most recent follow-up. The time to shunt failure was defined as the time between initial shunt placement and any subsequent shunt operation or death related to shunt failure.

Shunt failure was defined as a subsequent shunt-related operation for any reason, including infection, shunt obstruction, subdural collection, abdominal complication such as CSF pseudocyst, or death known to be related to shunt failure or infection. We used standard treatment success criteria to determine the adequacy of shunt function: a shift in head circumference growth to a normal or less-than-normal rate, as plotted on a standard growth chart; decompression of the anterior fontanel; relief from symptoms of elevated intracranial pressure (such as irritability and vomiting); resolution of abnormal eye findings (for example, sunsetting or cranial nerve VI palsy); and a decrease or arrest in ventriculomegaly as determined on
Shunt survival after ETV

ultrasonography or CT scanning by using the Evans ratio or frontal-occipital horn ratio, respectively. These are the same criteria for success that we have previously reported for endoscopic treatment. Shunt infection was determined by CSF profile, Gram stain, and culture result as well as clinical picture. Open or infected incisions and exposed shunt hardware from skin erosion were included as shunt infections. The criteria for diagnoses and clinical indications for treatment were consistent among all groups and over the period of the study.

Statistical Analysis

We analyzed time to shunt failure using the Kaplan-Meier method to construct survival curves and Cox proportional hazards regression modeling. Our primary objective was to determine if significant differences existed in time to shunt failure depending on what, if any, previous endoscopic treatment the child had received before VP shunt insertion.

Patients were divided into the following groups for analysis: 1) primary nonselective VP shunt placement without endoscopy (255 patients); 2) immediate VP shunt placement at the time of aborted ETV attempt without CPC (340 patients); 3) immediate VP shunt placement after aborted ETV attempt with CPC (30 patients); 4) VP shunt placement following ETV failure (141 patients); 5) VP shunt placement following CPC or ETV-CPC failure (154 patients). Preliminary analysis suggested that there was little difference between Groups 2 and 3 (p = 0.69, log-rank test) and Groups 4 and 5 (p = 0.97, log-rank test). Therefore, our analyses were limited to comparing differences among 3 treatment groups: primary nonselective VP shunt placement, immediate VP shunt placement after aborted endoscopy, and VP shunt placement after completed, but failed, endoscopy.

We performed risk-adjusted analyses to account for possible confounding differences among these groups. Age at VP shunt insertion and etiology of hydrocephalus (myelomeningocele, postinfectious, nonpostinfectious, other/unknown), both known to have some prognostic effect on hydrocephalus treatment, were included in a multivariate Cox regression model. We also considered adjusting for the patency of the cerebral aqueduct (open, closed, or unknown) and presence of preptontine cisternal scarring (yes, no, or unknown), which were determined by direct inspection at the time of endoscopy, as we have demonstrated these to be independent factors that affect the likelihood of ETV success. We decided, however, not to include these latter 2 variables in the final model because they were possibly confounded with the use of endoscopy (they were almost never assessable in patients who did not undergo endoscopy), and it would therefore not be possible to provide any independent interpretation of these variables. The proportional hazards assumption for each independent variable was confirmed by visual examination of survival curves (for categorical variables) and assessment of partial residual plots as a function of time (for all variables). All variance inflation factors were less than 3, suggesting no concerning collinearity among the variables in the multivariate model. The analyses were repeated using time to death (from any cause) and time to shunt infection as the dependent variable. All analyses were done with SPSS Advanced Statistics 17.0 (SPSS Inc.).

Results

Patient Characteristics

The characteristics of the 900 patients analyzed are shown in Table 1. Among the 3 treatment groups, there was no significant difference in age at shunt insertion (p = 0.8, ANOVA), but the distribution of etiologies was statistically different (p < 0.001, chi-square). Postinfectious hydrocephalus accounted for more than 78% of the group with abandoned ETV and immediate shunt placement.

Patient Follow-Up

Shunt failure was known to occur at some point in 299 patients. The mean follow-up time for the 601 patients who were not known to have had shunt failure was 28.7 months (median 18.8 months, interquartile range 4.1–46.3 months). The duration of follow-up was less than 6 months for 179 patients; 31 of these were known to have died of causes that were thought to be unrelated to shunt malfunction or infection. Thus 148 patients (16.4%) were lost to follow-up before 6 months after shunt placement. Follow-up data for more than 1 month were available for 536 (89.2%) of those with no known shunt malfunction.

Mortality

There were 13 known deaths from any cause within 30 days after VP shunt placement, for an overall operative mortality of 1.4%. Ten of these deaths did not appear to be related to shunt failure, and 3 occurred in the context of shunt failure. Of 99 confirmed deaths, 6 were directly attributed to shunt failure, including 2 shunt infections, one on postoperative Day 1, and the other on postoperative Day 545.

Patients with abandoned or failed endoscopic procedures did not have a higher operative mortality for shunt placement than those who did not undergo endoscopy, and there was actually a trend toward a lower mortality rate in these cases (Fig. 1) (p = 0.07 by log-rank and p = 0.14 by Cox regression adjusted for age and etiology).

Shunt Failure

For the entire sample, the shunt survival rate at 6 months, 1 year, 2 years, and 5 years was 74.3%, 69.5%, 64.6%, and 56.5%, respectively (Kaplan-Meier method). Of 299 shunt failures, 206 (68.9%) occurred within 180 days of placement. Etiology did not have a clear impact on shunt survival, with no significant difference in failure between infants with PIH and myelomeningocele and those with nonpostinfectious hydrocephalus (p = 0.91, log-rank).

Compared with those who were treated with primary shunt placement without endoscopy, survival analysis demonstrated a lower risk of shunt failure for those who underwent shunt placement after a completed but failed
endoscopy (p = 0.008, log-rank) with a hazard ratio (adjusted for age at shunting and etiology) of 0.72 (95% CI 0.53–0.98), p = 0.03 (Fig. 2). There was no significant difference between patients shunted nonselectively with no endoscopy and those shunted at the time of an abandoned endoscopy attempt (adjusted HR 1.14, 95% CI 0.86–1.51, p = 0.35).

Given that PIH accounted for a disproportionate number of patients who underwent shunt placement at the time of the abandoning of an ETV attempt (78.4%), there was concern that this could have created selection bias. The ventricles of PIH patients treated with shunt placement after ETV failure would have been less involved by ependymal scarring and destruction than their counterparts in whom the ETV attempt had been abandoned due to distorted anatomy or poor visibility. Because PIH composed such a distinct and dominant group, we subsequently performed a stratified subgroup analysis of all PIH cases (578 cases) (Fig. 3A) and all other etiologies with PIH excluded (322 cases) (Fig. 3B). This demonstrated a robust effect of prior ETV in the PIH group (adjusted HR 0.55, 95% CI 0.36–0.85, p = 0.007) but no significant effect for the noninfectious etiologies (adjusted HR 0.98, 95% CI 0.64–1.50, p = 0.92). For both the PIH group and all others, there was no statistically significant difference in shunt survival between those who underwent primary shunt placement and those who underwent shunt placement at the time of an aborted endoscopy (p = 0.38 and p = 0.89, respectively). Thus, the PIH group entirely accounted for the positive effect of previous ETV on shunt survival in the overall group, and there appeared to be no such effect among the other etiologies.

**Shunt Infection**

Among the 900 new shunt placements, there were 119 total known shunt infections. The infection rate at 30 days was 13.2% (95% CI 10.5–16.0%). The Kaplan-Meier survival curve for time to death from any cause after VP shunt placement is shown in Fig. 1. The curve for time to shunt failure is shown in Fig. 2.
Shunt survival after ETV

Days, 90 days, 6 months, 1 year, and 2 years was, respectively, 5.7%, 9.5%, 11.7%, 13.3%, and 15.2% (Kaplan-Meier method). It is notable that, although the majority of known infections occurred in the first 6 months, late shunt infections continued to occur over the 7-year time span at a rate of about 1% per year (Fig. 4). Of 119 shunt infections, 10 presented primarily with wound infection or breakdown or skin erosion over the shunt hardware, a complication typically associated with severe malnutrition.

Survival analysis demonstrated no difference in shunt infection among any of the 3 treatment groups (primary shunt placement, shunt placement after abandoned endoscopy, and shunt placement after failed endoscopy) (p = 0.94, log-rank). As with shunt failures, it is notable that the infection rate was not higher among infants with PIH or myelomeningocele, for whom CSF contamination might be more likely, when compared with those with nonpostinfectious hydrocephalus of other causes (p = 0.17, log-rank).

Discussion

The purpose of this study was to investigate whether, compared with patients treated with primary shunt placement, those with failed or abandoned endoscopic treatment might have an altered incidence of shunt malfunction or infection over time. It was our hypothesis that prior completed ETV or CPC might decrease the risk of shunt failure, and it was our hope that an intention to treat by endoscopy in all patients did not increase the risk of shunt infection or failure. These data demonstrate no effect of an abandoned ETV attempt on shunt survival or infection risk relative to primary shunt placement without endoscopy. Interestingly, patients with PIH who underwent shunt placement following failure of a completed ETV had significantly better shunt survival than those in whom a shunt was placed as a primary treatment or at the time of abandoned ETV, while no such effect was observed among those with noninfectious etiologies. Although we had thought that CPC might decrease the risk of future shunt malfunction, this study failed to demonstrate such an effect, and CPC did not increase the risk of future shunt infection. That all the significant effect of prior ETV came purely from the PIH group limits the conclusions that can be drawn.

Patients with abandoned or failed endoscopic procedures did not have a higher operative mortality for shunt placement than those without endoscopy, and there was actually a trend toward a lower mortality in these cases. In geographically defined cohort studies with very successful follow-up, we have previously reported that childhood mortality for infants with both myelomeningocele and PIH (the 2 most common individual etiologies of hydrocephalus at CCHU) is significantly greater than for their...
unaffected peers. The under-5-year mortality among infants treated for myelomeningocele and those treated for PIH was 37% and 30%, respectively, compared with the overall reported childhood mortality of 16% in Uganda. We demonstrated that most deaths were due to common treatable conditions unrelated to hydrocephalus or its treatment and that survival in myelomeningocele patients was equivalent to that in unaffected Ugandan children in the context of a community-based rehabilitation program. Thus, the mortality rate observed in the present study was completely expected.

Gallo et al. suggested that previous ETV might decrease future shunt malfunction, and Shim et al. suggested that simultaneous ETV and shunt placement had the same effect. But, these reports involved small numbers of patients and lacked statistical significance. Our findings in a much larger population fail to indicate a statistically significant protective effect of a successfully completed ETV (with or without CPC) against future shunt malfunction in patients with noninfectious causes of hydrocephalus. Surprisingly, a robust effect was observed in the PIH group. There are a few possible explanations for and interpretations of our findings:

**Could Previous ETV With or Without CPC Have a Physiologically Protective Effect Against the Failure of a Subsequently Implanted VP Shunt?**

Among patients undergoing endoscopy for hydrocephalus treatment during the study period, 60.4% were younger than 6 months, and 85.2% were younger than 12 months of age. Young age is a negative factor for ETV success and this may be related to the evolving efficacy of CSF absorption in infants. This had formed the basis for our original hypothesis that CPC might improve the outcome for ETV in infants, in that an even temporary reduction in the rate of CSF production might balance any residual “communicating” hydrocephalus (from insufficient absorption) that may remain after ETV had successfully bypassed the “obstructive” component. It is possible that a persistently patent ETV might become more effective at treating hydrocephalus over time, rendering a subsequent shunt malfunction clinically irrelevant. However, the data presented here failed to support this in patients with hydrocephalus of noninfectious causes. Although it is possible that an initially failed ETV may allow some children to become shunt-independent over time, it seems equally possible that a patent ETV at the time of shunt placement may close as a result of ventricular decompression from the shunt. Finally, if ETV itself decreased the risk of future shunt malfunction, the effect should be observed in the noninfectious etiologies. That this would only be observed for PIH is difficult to explain.

Likewise, we had considered the possibility that for some patients, CPC alone could have provided some protection against future shunt failure. It seemed possible that CPC might become sufficient to treat a “communicating” hydrocephalus after the child is older and CSF absorptive mechanisms have become sufficient to achieve the necessary balance. But there was no significant difference in shunt survival between those with failed ETV alone and those with failed ETV-CPC. Alternatively, CPC, by reducing the choroid plexus to a line of scar tissue, should prevent ventricular catheter obstruction by choroid plexus, which is often regarded as the most common cause of shunt malfunction. However, we found no difference in shunt survival in regard to whether CPC had been performed, which fails to support this attractive hypothesis.

*Why Did a Prior ETV Appear to Protect Against Shunt Malfunction in the PIH Group?*

Patients with completed ETVs are distinct from those in whom completion of the procedure was not possible, and the latter group might have had an intrinsically higher risk of shunt failure. This initially seemed less likely, since the treatment groups represented different epochs of treatment and, within each epoch, treatment was offered nonselectively. Initially, all patients were treated with CSF shunting, and subsequently all patients were treated with attempted ETV or ETV-CPC in an unselected manner. But patients with PIH are a heterogeneous group with varying degrees of prior ventricular destruction, those with the worst involvement accounting for the majority of those for whom ETV had been abandoned. This raises a strong possibility of selection bias within the PIH group. However, it is important to observe that there was no significant difference in outcome between patients who underwent shunt placement without endoscopy and patients treated with shunt placement at the time of an aborted ETV attempt. The latter group (78.4% of whom had PIH) primarily included those with severe anatomical distortion and significant cisternal scarring. If the improved shunt outcome following failed ETV were only from the aforementioned effect of selection, then one would anticipate a higher shunt failure risk in the remaining group (that is, those in whom ETV was abandoned), than that observed in patients nonelectively treated with shunt placement without endoscopy, which would have included all patients. That this was not the case suggests a possibly real protective effect of the prior ETV. However, as noted above, it is counterintuitive that such an effect would be confined to those with PIH. It is possible that endoscopic fenestration of membranes in PIH patients at the time of attempted ETV and shunt placement could have improved the ultimate shunt outcome in a manner sufficient to account for the equivalence of outcome in the group of patients treated with primary shunt placement and the group that underwent shunt placement at the time of an abandoned ETV.

*Was There a Protective “Second-Surgery Effect” in Which There was Some Advantage to the Second, Delayed Procedure of Shunt Placement?*

This could have been the case for those patients with PIH whose CSF at the time of the initial operation might have been contaminated or might have contained debris that had cleared by the time of the second operation. It would not be an anticipated benefit for those with noninfectious etiologies.

*Were There Other Unaccounted Residual Confounders?*

Given that the patient groups were treated in different...
epochs, it is possible that the more recently treated endoscopy group received better overall medical care because the medical team had acquired more experience over the study period. Given the relative technical ease of shunt insertion, it seems unlikely that better surgical skill was contributory. As well, there was no obvious shunt survival advantage to those who were underwent shunt placement at the time of aborted endoscopy, who theoretically should also have benefited if there was an improvement in overall care for the more recent patients.

Also, this effect would have been the same regardless of hydrocephalus etiology. Another possible confounder is shunt location and insertion technique. Shunts placed at aborted, or after failed, endoscopy were inserted frontally, while primary shunts were placed occipitally. But, this would have been true for patients with infectious and noninfectious etiologies of hydrocephalus, alike. In addition, shunt location is unlikely to have had an effect, since the frontally placed shunts that were placed after aborted endoscopy did not show a survival advantage compared with the shunts placed as a primary treatment. Also, the advantage of one shunt location over the other remains unconfirmed. The same is true for any advantage from endoscopic assistance of ventricular catheter placement, which was used in both the abandoned endoscopy and completed endoscopy groups. In addition, endoscopically assisted ventricular catheter placement has been previously found to be of no benefit in avoiding shunt malfunction.

Conclusions

We report, in a large population of patients treated with CSF shunting for hydrocephalus, that the paradigm of primarily attempting ETV with or without CPC had no adverse effect on mortality or on subsequent shunt survival or infection risk. An apparent benefit of prior ETV on shunt survival was observed only in patients with PIH, but this seems most likely an artifact of selection or timing of the shunt placement arising from the inherent heterogeneity of ventricular damage within that group. The anticipated benefit of CPC in preventing future ventricular catheter obstruction was not observed.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Warf. Acquisition of data: Warf, Bhai, Mugamba. Analysis and interpretation of data: Warf, Bhai, Kulkarni. Drafting the article: Warf. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Warf. Statistical analysis: Warf, Kulkarni. Administrative/technical/material support: Warf, Bhai, Mugamba. Study supervision: Warf.

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