International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 12, December 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.12.2024.82

ORIGINAL RESEARCH

Antibiotic or silver versus standard ventriculoperitonealshunts (BASICS): single-blinded, randomised trial and economic evaluation

[1]Dr. Akash Mishra, [2]Dr. Dushyant Singh Solanki

[1]Assistant Professor, Department of Neurology, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India
[2]Assistant Professor, Department of General Surgery, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India

Corresponding Author
Dr. Dushyant Singh Solanki
Assistant Professor, Department of General Surgery, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India

Received Date: 19 October, 2024 Accepted Date: 24 November, 2024

ABSTRACT

Background: Insertion of a ventriculoperitoneal shunt for hydrocephalus is one of the commonest neurosurgical procedures worldwide. Infection of the implanted shunt affects up to 15% of these patients, resulting in prolonged hospital treatment, multiple surgeries, and reduced cognition and quality of life. Our aim was to determine the clinical and cost-effectiveness of antibiotic (rifampicin and clindamycin) or silver shunts compared with standard shunts at reducing infection. **Methods:** In this parallel, single-blind, randomised controlled trial, we included patients with hydrocephalus of any aetiology undergoing insertion of their first ventriculoperitoneal shunt irrespective of age at adult and paediatric neurosurgery in Saraswathi Institute of Medical Sciences, Hapur. Patients were randomly assigned (1:1:1 in random permuted blocks of three or six) to receive standard shunts (standard shunt group), antibiotic-impregnated (0•15% clindamycin and 0•054% rifampicin; antibiotic shunt group), or silver-impregnated shunts (silver shunt group) through a randomisation sequence generated by an independent statistician. All patients and investigators who recorded and analysed the data were masked for group assignment, which was only disclosed to the neurosurgical staff at the time of operation. Participants receiving a shunt without evidence of infection at the time of insertion were followed up for at least 6 months and a maximum of 2 years. The primary outcome was time to shunt failure due the infection and was analysed with Fine and Gray survival regression models for competing risk by intention to treat. **Interpretation:** The BASICS trial provides evidence to support the adoption of antibiotic shunts in patients who are having their first ventriculoperitoneal shunt insertion. This practice will benefit patients of all ages by reducing the risk and harm of shunt infection.

INTRODUCTION

Hydrocephalus affects one in every 500 births.[1] It also affects children and adults of all ages and can be secondary to different causes including haemorrhage, trauma, infection, and intracranial tumours.[2] A systematic review and meta-analysis[3] reported theprevalence of hydrocephalus to be 88 cases in 100 000 in children (aged ≤18 years), 11 cases in 100 000 in adults (aged 19– 64 years), and 175 cases in 100 000 in elderly people (≥65 years).[3] The commonest treatment for hydrocephalus is a ventriculoperitoneal shunt, which comprises proximal (ventricular) and distal (peritoneal) silicone catheters joined by a valve to drain CSF from theventricles into the peritoneal cavity. Insertion of a ventriculoperitoneal shunt for hydrocephalus is one of the commonest neurosurgical procedures worldwide.[4] Failure of this shunt due to infection occurs in 7–15% of patients.[5,6] Episodes of infection have a major impact on patients and are expensive to manage, requiring prolonged hospital treatment, antibiotics, and surgery to remove the infected shunt and to place a new one once the infection has been treated. Nevertheless, a health economic analysis from a UK perspective has not been done so far. Shunt infection affects health-related qualityof life, cognitive function,[7] and survival, with the numberof infections per patient throughout their lifetime being an independent predictor of

DOI: 10.69605/ijlbpr_13.12.2024.82

death.[8]

Antibiotic-impregnated shunt catheters have been introduced as a means to reduce infection in addition to standard procedures (eg, prophylactic intravenous anti- biotics) to prevent infection at the surgical site. There are three types of shunt catheter: standard, antibiotic- impregnated (0·15% clindamycin and 0·054% rifampicin), and silver-impregnated. Systematic reviews and meta- analyses[9,10] did not find any high-quality evidence to support the comparative effectiveness of these catheter types at reducing shunt infection. Consequently catheter choice varies globally, with selection based on the preference of the neurosurgeon and costs.

We coordinated the British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts (BASICS) multicentre randomised controlled trial to assess the clinical efficacy and cost-effectiveness of antibiotic and silver shunts at reducing shunt failure dueto infection, compared with standard shunts in patients undergoing insertion of their first ventriculoperitoneal shunt for hydrocephalus.

METHODS

Study design

In this parallel, multicentre, single-blind, randomised controlled trial we compared standard, antibiotic, and silver shunts in patients undergoing insertion of their first ventriculoperitoneal shunt for hydrocephalus. Trial sites were 21 regional adult and paediatric neurosurgery centres in the UK and Ireland (appendix pp 6–7). Ethics approval was obtained from the North West Greater Manchester Research Ethics Committee (reference number 12/NW/0790). The trial protocol is available online and has been published previously[11] (substantial amendments are detailed in the appendix p 55).

Participants

To participate in randomisation in the trial, patients could be of any age and have hydrocephalus of any aetiology requiring a first ventriculoperitoneal shunt. Patients with failed primary endoscopic third ventriculostomy, previous indwelling external ventricular drain, and indwelling ventricular access device were included. Patients were excluded if they had evidence of active and ongoing CSF or peritoneal infection; a previous indwelling ventriculoperitoneal shunt; multiloculated hydrocephalus requiring multiple shunts or neuroendoscopy; known allergy to rifampicin, clindamycin, or silver; or if a ventriculoatrial or ventriculopleural shunt was planned. Written informed consent was obtained for all patients; minors provided written consent whenever possible. Consent for adults lacking capacity was obtained from a consultee, usually the next of kin, or an independent health-care professional, and it was later sought again from the participant once capacity was regained.

Randomisation and masking

Patients were randomly assigned to receive stan- dard shunts (standard shunt group), antibiotic- impregnated shunts (antibiotic shunt group), or silver-impregnated shunts (silver shunt group) in random permuted blocks of three and six (1:1:1). The randomisation sequence was generated by an independent statistician not otherwise involved in the trial and was stratified by neurosurgical unit and age group (adult or paediatric, defined according to unit practice). The randomisation was disclosed in the operating theatre at the time when the shunt was required using opaque, tamper-proof, sealed envelopes that were opened by tearing perforated edges. Envelopes were prepared and sealed by the independent statistician and were then sent by the trial team to the study site, where they were stored in the operating theatre, ready for use. The shunts had different colours, so it was not possible to mask the neurosurgeon and operating staff. Shunt type was not recorded in the operating record and was not disclosed outside the operating room. All investigators and statisticians who recorded and analysed data were masked to shunt assignment. Training on non- disclosure of shunt type was provided to all investigators. All shunt types were used in accordance with the manufacturer's instructions for their intended purpose. Patients were also masked to the type of shunt inserted.

Procedures

Data were collected at baseline, preoperative assessment, randomisation (first surgery), early postoperative assess- ment, first routine postoperative assessment, 12-weekly follow-up assessments, subsequent routine postoperative assessments, and, where applicable, at unscheduled visits and admissions, and at shunt revision and removal (appendix p 8). All patients received prophylactic antibiotics at the time of shunt insertion as per standard neurosurgical practice. All other parameters relatedto the surgical technique of shunt insertion (eg, choice of skin preparation, hair removal or not, number and seniority of operating neurosurgeons, rank on the operating list) were recorded but not standardised and were undertaken according to the practice of each participating neurosurgical centre. For patients requiring a first shunt revision after insertion, sites recorded data on clinical presentation (eg, temperature, headache, lethargy, meningism, consciousness level, wound erythema), peripheral white blood cell count, C-reactive protein concentrations, microbiological analysis of CSF (microscopy and culture), and type of treatment initi- ated (eg, antibiotics prescribed, shunt removed). Patients were followed up for a minimum of 6 months and a maximum of 2 years, depending on the time of random- isation. The types of data collected at each stage and methods used are detailed in the online study protocol.

DOI: 10.69605/ijlbpr_13.12.2024.82

Outcomes

The primary outcome was time to shunt failure due to infection, assessed by a masked central review panel comprised of our study's chief investigator (CLM or delegate [MDJ] for participants treated by the chief investigator) and trial microbiologist (JCH). On the basis of data on clinical presentation and type of treatment given, the shunt failure was classified as being due to infection or not on the basis of five infection definitions (panel). The secondary outcomes were time to removal of the first shunt due to suspected infection as defined by the treating neurosurgeon at the time of first revision; time to shunt failure by any cause; reason for shunt failure as classified by the treating neurosurgeon (infection; mechanical [blockage of any component such as the valve or catheters]; patient [unrelated medical condition such as appendicitis]; or functional [change of valve for symptomatic overdrainage or underdrainage of CSF, such as change from a fixed-pressure valve to a programmable valve]); types of bacterial shunt infection; time to shunt infection after first clean revision as classified by central review; and quality of life measured using the Hydrocephalus Outcome Questionnaire.12 The secondary health outcomes for the economic analysis were incremental cost per shunt failure by any cause averted and per quality-adjusted life-year (QALY) gained, using the EQ-5D-3L, EQ-5D-3L (proxy), or EQ-5D-3L-Y versions of the EQ-5D health-related quality-of-life questionnaire. Data on complications and serious adverse events were collected (see the online protocol).

Statistical analysis

A trial steering committee, mostly comprising independent members who viewed reports in which treatment assignment was concealed, and an independent data monitoring committee viewing unblinded reports reviewed the trial regularly to assess conduct, progress including rates of shunt infection, and safety. The sample size estimate for the primary outcome was done via the method described by Pintilie13 with the following assumptions: (1) shunt failure due to infection was the event of interest, with all other reasons for failure representing a competing risk; (2) the incidence of infection would be 8% in the standard shunt group5 and 4% in each of the impregnated shunt (antibiotic or silver) groups; (3) the competing risk event rate would be 30%; and (4) 5% of patients would be lost to follow- up. On the basis of these assumptions, a total sample size of 1200 patients with 119 shunt failures due to infection showed sufficient statistical power (88%) with leverage for a reduced event rate. An interim analysis was planned after 50% of the total events had been observed, in accordance with the Haybittle-Peto boundary.14 The incidence of infection showed that the majority of events occur within 1 month of shunt insertion (ie, was not exponentially distributed), and that the incidence of infection, competing risk, and loss to follow-up were lower than expected. The independent data monitoring committee reviewed the sample size calculations and recommended increasing recruitment to a target population of 1606 patients with 101 shunt failures due to infection to provide 80% power; the trial steering committee agreed. The early occurrence of events and assumption of exponential risk were managed in the Pintilie assumptions13 by reducing the event accrual and follow-up rates to 1 month.

The analysis was done according to a prespecified statistical analysis plan. Amendments to the plan were considered and implemented by a masked statistician, which included masked collection and summary of the data before database lock. Outcomes were analysed according to the intention-to-treat principle and safety analyses according to the type of shunt in situ. To adjust for the three treatment groups, a p value of 0•025 was considered significant and 97•5% CIs were used throughout. Outcome analysis, with shunt failure due to infection as the event of interest, used Fine and Gray15 survival regression models with cause-specific hazard ratios (csHR) and subdistribution hazard ratio (sHR) presented.16,17 Cox regression models were used to analyse time to shunt failure of any cause. The assumption of proportionality for time to event outcomes was checked using Schoenfeld residuals. Reason for shunt failure is presented descriptively and with a χ^2 test. Types of organisms cultured from CSF are presented descriptively with frequency tables, no formal statistical analyses were done. Quality-of-life outcomes were analysed using mixed models for repeated measures. All survival models were adjusted for the age category of the recruiting site (paediatric or adult), with adult sites further categorised by age above 65 years. Due to the dependency between age group and study site, adjusting models by both covariates was not possible. Instead, age group was used in preference to study site because of its prognostic value. Analyses for the primary outcome and safety were validated by independent programming from the point of raw-data extraction. All analyses were done with the SAS software (version 9.4) with SAS/STAT package 14.3. The trial was registered with ISRCTN 49474281.

RESULTS

Between June 26, 2013, and Oct 9, 2017, we assessed 3505 patients for eligibility and randomly assigned 1605 to the study groups (536 to the standard shunt group, 538 to the antibiotic shunt group, and 531 to the silver shunt group; figure 1). One patient was erroneously randomised twice and so data from the first randomisation only were used. 53 participants subsequently withdrew from follow-up, of whom 24 continued to provide routinely collected data. The characteristics of the three groups were similar at baseline (table 1, appendix pp 11– 12). 1601 (99·8%)

DOI: 10.69605/ijlbpr_13.12.2024.82

patients had a shunt inserted and 1585 (98·8%) received the correct allocated shunt (figure 1). Patients who did not receive a shunt (n=4) or who had an infection at insertion (n=7) were not included in the primary analysis. The number of patients included in the primary analysis was 533 in the standard shunt group, 535 in the antibiotic shunt group, and 526 in the silver shunt group. The median follow-up time for patients assessed for the primary outcome was 22 months (LQ– UQ 10–24, min to max 0–24; n=1594).

398 (25%) of the 1594 followed up patients had revision operations, with 75 (5%) being centrally classified as having shunt infections (table 2). Compared with the standard shunt, the antibiotic shunt decreased the incidence of shunt failure due to infection over time (csHR 0·38, 97·5% CI 0·18–0·80, p=0·0038; table 3). Silver shunts were comparable with standard shunts (0·99, 0·56–1·74, p=0·96) in this respect. Figure 2 shows the cumulative incidence of failure due to infection by shunt group. 53 (71%) of 75 centrally assessed infections were classified as definite (culture- positive).

Of the 398 revision operations, 78 (5%) were defined by the treating neurosurgeon as being caused by a suspected infection (table 2). Antibiotic but not silver shunts were associated with a significant decrease of failure due to infection when compared with standard shunts (table 3). The reason for revision was classified by central review (primary outcome) and treating neurosurgeon (secondary outcome) as infection or no infection, and this classification was the same in 381 (96%) revisions (appendix p 13).

Kaplan-Meier curves for time to shunt failure for any cause showed no significant difference between antibiotic or silver and standard shunts (table 3, appendix p 13). The number of shunt failures was similar between the three groups (table 2); however, the underlying reason differed when comparing patients who had standard shunts with those who had antibiotic shunts (p=0·024), but not those with silver shunts (p=0·71; appendix p 14). Patients with antibiotic shunts had fewer infections but a higher frequency of mechanical shunt failure than the other two groups (appendix p 14).

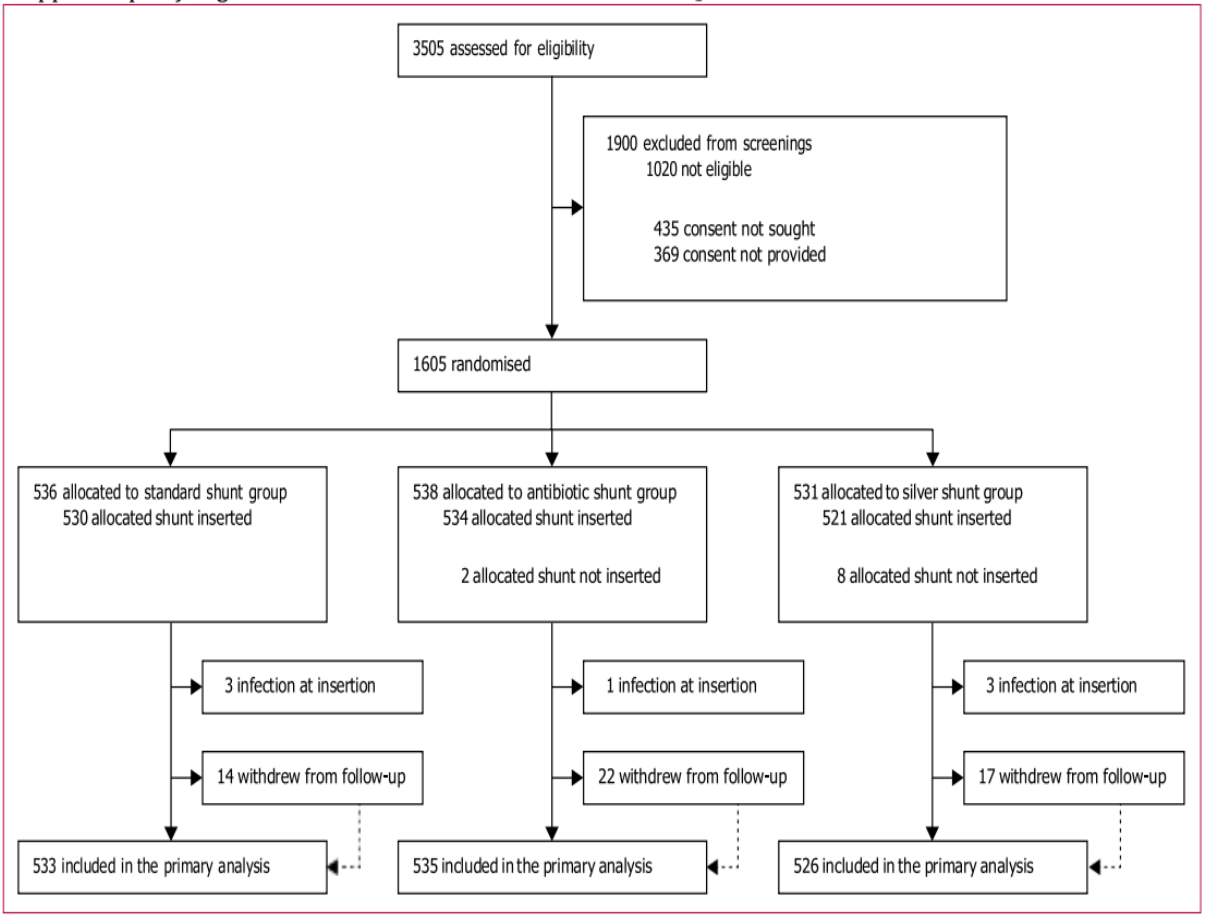
Staphylococcus aureus (17 [30%] of 56 infections) and coagulase-negative staphylococci (22 [39%]) accounted for most organisms cultured from infected shunts (appendix p 15). Culture results showed a reduction in staphylococcal and Gram-positive infections in patients with antibiotic shunts compared with those who had standard or silver ones. Patients with all three shunt types had a similar number of Gram-negative infections. The proportion of culture-positive infections was lowest in patients with antibiotic shunts compared with patients from the other two groups (table 2). The remaining infections were identified by the central review panel on the basis of CSF white-cell counts, clinical features, and blood parameters (table 2).

In patients whose first revisions were not due to infection (n=323) as assessed by central review, the overall incidence of subsequent revisions for any reason (infection and no infection) was 40% (n=126; appendix p 16), higher than in the full follow-up group (table 2). The overall incidence of infection was higher in this subgroup (20 [6%] of 323; appendix p 16) than in the full follow-up group. There was no significant difference in time to infection following the first clean revision when comparing either antibiotic or silver (table 3) with standard shunts.

The proportion of revisions of the first shunt for any cause (225 [38%] of 592 children, 118 [24%] of 499 adults younger than 65 years, and 55 [11%] of 503 adults aged 65 years and above; appendix p 17) and for infection (47 [8%], 23 [5%], and five [1%]; appendix p 17) varied by participant age group. Compared with children, over time adults younger than 65 years and adults aged 65 years and above had a significantly lower rate of shunt failure due to infection (<65 years csHR 0•55, 97•5% CI 0•31–0•97, p=0•0018; ≥65 years 0•12, 0•04–0•34, p=0•0019; table 3, appendix pp 18–19).

Schoenfeld residuals supported the assumption of proportionality for time to event outcomes. There were no serious adverse events. 654 adverse events were reported in 413 (26%) of all patients who received a shunt. The proportion of patients experiencing an event were similar across the three groups (standard 135 [25%], antibiotic 136 [25%], and silver 140 [27%]; appendix pp 20–21). Questionnaires, and results are therefore presented descriptively (appendix pp 50–51). In the cost-utility analysis, silver shunts were cheaper than antibiotic shunts (appendix p 49). Compared with standard shunts, silver shunts were £183 more expensive and yielded 0•096 additional QALYs overall, resulting in an incre- mental cost-effectiveness ratio of £1904 per QALY gained, and a probability of 0•52 of being cost-effective at a willingness to pay of £20 000 per QALY (appendix p 53).

DOI: 10.69605/ijlbpr_13.12.2024.82



	Standard shunt (n=536)	Antibiotic shunt (n=538)	Silver shunt (n=531)	Total (n=1605)
Age at randomisation, years				
Median (LQ–UQ)	42·5 (0·8–69·7)	43·9 (1·1–70·8)	41·1 (0·5–68·8)	42·5 (0·8–69·6)
Range	0·0–90·3	0·0–88·9	0·0–91·1	0·0–91·1
Age category				
Paediatric	200 (37%)	201 (37%)	198 (37%)	599 (37%)
Adult (<65 years)	174 (32%)	156 (29%)	172 (32%)	502 (31%)
Adult (≥65 years)	162 (30%)	181 (34%)	161 (30%)	504 (31%)
Gender				
Female	246 (46%)	260 (48%)	282 (53%)	788 (49%)
Male	289 (54%)	278 (52%)	249 (47%)	816 (51%)
Missing	1 (<1%)	..	..	1 (<1%)

Data are number of participants (%), unless otherwise specified.

Table 1: **Baseline characteristics of the intention-to-treat population**

DOI: 10.69605/ijlbpr_13.12.2024.82

	Standard shunt	Antibiotic shunt	Silver shunt	Total
Surgeries				
Patients eligible for primary outcome*	533	535	526	1594
No shunt removal or revision	403 (76%)	403 (75%)	390 (74%)	1196 (75%)
Shunt removal or revision (for any cause)	130 (24%)	132 (25%)	136 (26%)	398 (25%)
Reason for revision as classified by central review				
Patients revised for infection	32 (6%)	12 (2%)	31 (6%)	75 (5%)
CSF or peritoneal infection				
Definite (culture-positive)	22/32 (69%)	6/12 (50%)	25/31 (81%)	53/75 (71%)
Probable (culture-uncertain)	1/32 (3%)	..	2/31 (6%)	3/75 (4%)
Probable (culture-negative)	3/32 (9%)	3/12 (25%)	1/31 (3%)	7/75 (9%)
Possible (culture-uncertain)	1/32 (3%)	..	1/31 (3%)	2/75 (3%)
Clinically classified infection†	1/32 (3%)	..	..	1/75 (1%)
Shunt deep incisional infection	4/32 (13%)	3/12 (25%)	2/31 (6%)	9/75 (12%)
Patients revised for other reason (no infection)	98 (18%)	120 (22%)	105 (20%)	323 (20%)
Reason for shunt revision as classified by treating neurosurgeon				
Suspected infection	33 (6%)	15 (3%)	30 (6%)	78 (5%)
Revision for other reason (no infection)	97 (18%)	117 (22%)	106 (20%)	320 (20%)

Data are n, n (%), or n/N (%) of patients. *Randomised participants who did not receive a shunt (n=4) and had infection at time of insertion (n=7) were excluded from the primary outcome set (figure 1). †In one case the committee was unable to classify the infection, so the infection was clinically identified from the case report forms.

Table 2: **Summary and reasons for revision of first shunt according to catheter type and assessor**

DISCUSSION

In this trial of patients with hydrocephalus undergoing insertion of a first permanent ventriculoperitoneal shunt, 6% of those receiving standard shunts, 2% of those receiving antibiotic shunts, and 6% of those receiving silver shunts had an infection. Compared with standard shunts, antibiotic shunts were associated with a significantly lower incidence of infection, whereas silver shunts were not. This effect was present across all age categories. The risk of shunt infection was highest in children, reducing in adults, and being particularly low in the elderly. There are significant economic benefits for every shunt infection averted, although cost- effectiveness is greatest in those at highest risk.

The BASICS trial provided sound evidence on the use of antibiotic shunts to reduce infection. A previous randomised trial22 compared antibiotic with standard shunts, but was underpowered and did not show a significant difference in the risk of infection (relative risk 0•38, 95% CI 0•11–1•30; p=0•12).22 Additionally, systematic reviews and meta-analyses9,10 did not find any high-quality evidence to support the comparative effectiveness of antibiotic shunts at reducing infection. Silver catheters have only been evaluated for use in temporary external ventricular drains, not permanently implanted shunts. A randomised trial23 of external ventricular drains (silver vs standard) reported a reduction in infection from 21% (30 of 140 patients with a standard drain) to 12% (17 of 138 patients with a silver drain; p=0•042), although this proportion is much higher than the UK's national reported infection rate (9%).24 The BASICS trial was therefore conceived to evaluate both antibiotic and silver shunts, which might otherwise have been widely introduced into routine clinical practice despite a lack of firm evidence of their efficacy. The results of our trial show that antibiotic shunts have good clinical and cost-effectiveness and will inform neurosurgery practice and shunt choice for the benefit of patients. Correctly diagnosing shunt infections when the CSF is culture-positive is straightforward, but this situation only applies to about 70% of cases. When the CSF is culture- negative, the treating neurosurgeon must consider other parameters including CSF white-cell counts, clinical symptoms and signs, and previous treatment with antibiotics. In these circumstances, removal of the shunt and antibiotic treatment often resolve the presumed infection and the patient recovers. The classification of shunt infection in our study was determined by the central review committee (table 2), and the proportion of culture-positive infections was 69% in patients with standard

DOI: 10.69605/ijlbpr_13.12.2024.82

shunts, 50% in those with antibiotic shunts, and 81% in those with silver shunts. There was a reduced incidence of culture-positive infections with antibiotic shunts. Our analysis allowed for culture-negative infections to be included when there was sufficient supporting clinical evidence of shunt infection. This inclusion was possible because we postulated that the presence of antibiotic and possibly silver shunts might reduce the ability to culture organisms from infected shunts. Our study showed an even greater effect favouring antibiotic shunts when only culture-positive infections were analysed. The reduction of infections seen is consistent with the expected microbiological spectrum inhibited by the antibiotic shunts, which are especially active against Gram-positive organisms, and were designed to prevent infection by Staphylococcus species. The culture results show a large reduction in staphylococcal infection when antibiotic shunts were present, compared with standard and silver shunts, which account for most of the reduced infections. Patients with all three shunt types had a similar number of Gram-negative infections, supporting the biological plausibility of our results. It should be noted that the overall incidence of shunt failure was the same for all groups, although infection was reduced in patients with antibiotic shunts. When infection is discounted as a cause of shunt failure, clean, non-infected revisions were slightly more frequent in patients with antibiotic shunts. The cause is unclear, but one hypothesis is that the antibiotic catheters might convert a true infected shunt revision into an apparently clean shunt revision. This masking might occur because pathogens with low virulence are restricted to a biofilm in the valve (which is not impregnated) that does not cause detectable changes in the CSF (such as increased white-cell count), as there is no ventriculitis and the bacteria are few or unable to grow in the presence of the eluted antibiotics. However, changes in CSF composition and flow (such as debris or high protein) might block the intricate valve mechanism. Our study was not powered or designed to answer this question directly, but analysis of the CSF samples collected in BASICS might lead to improved pathogen detection.

Nevertheless, from the patient's perspective, although mechanical shunt revision still requires surgery which could impact on quality of life, the hospital admission is short, prolonged antibiotics are not required, and patients recover faster with fewer long-term neurological sequelae than if their shunts become infected.

Complications associated with shunt failures are expensive to manage.25–27 Economic analyses suggest that the use of impregnated shunts that result in fewer complications, even if more expensive to purchase, could be cost-effective or yield cost savings.10,28,29 The cost- effectiveness analysis in BASICS estimated that although antibiotic shunts cost twice as much as standard shunts, they are expected to be cost-effective overall. Nevertheless, on the basis of the primary economic outcome, this estimate might be at the expense of additional cases of shunt failures (for any reason) associated with the use of silver and antibiotic shunts compared with standard ones. The secondary economic outcome based on the incremental cost per shunt infection averted is relevant because a reduced incidence of infection is expected to be associated with reduced need of further surgery and prolonged hospital care. Standard shunts were superior to silver shunts but were inferior to antibiotic shunts, The cost-utility analysis was limited by missing data and by the exclusion of participants who were at highest risk of shunt infections.

The strengths of our study are that (1) infections were centrally classified by researchers masked to treatment allocation, thereby removing the risk of bias by the treating neurosurgeon; (2) participant retention was very high because of the nature of the intervention and the primary outcome (patients with infected shunts are always re-admitted to hospital); (3) patient withdrawal was low (53 [3%]) so it is unlikely that shunt failures due to infection were undetected; (4) participants were recruited across the whole of the UK and Ireland to encompass all ages and socioeconomic classes; (5) the study population was large; and (6) the results have wide generalisability because we did not mandate a specific surgical technique for shunt insertion.

Some limitations of our trial should be noted. First, it was not possible to mask the treating neurosurgeon to the shunt type because the physical appearance of the shunts is distinctive. The shunt type was concealed from the patient and was not recorded in the patient records. Most shunt revisions and removals for infection happen as emergencies and are managed by the emergency neurosurgery team. Therefore, the likelihood of the same neurosurgeon who inserted the shunt being involved in the decision to remove it was low, considering the work rotas of neurosurgical staff. Furthermore, there was high agreement between shunt infections classified by the treating neurosurgeon and central assessment (96%), suggesting that any bias coming from the treating neurosurgeon did not affect the conclusions. Second, ventriculoatrial and ventriculopleural shunts were excluded, although we postulate that the results are translatable to patients with those shunt types. Finally, the low proportion of patient-reported outcomes restricted the analysis of the effect of shunt infection on patients, and the reliability of the cost-utility analysis.

The BASICS study is the largest prospective randomised study of patients with shunts for hydrocephalus worldwide. The blood and CSF samples from study participants will be used for future research into biomarkers for infection and host response. Data on hydrocephalus aetiology, surgical techniques, types of valves, and technology used for shunt insertion will be analysed and used to develop recommendations and health-care policy for patients

DOI: 10.69605/ijlbpr_13.12.2024.82

receiving ventriculoperitoneal shunts. Antibiotic shunts would reduce the risk of infection and be substantially cost-effective, and thus they should be the first choice for patients with hydrocephalus undergoing insertion of their first ventriculoperitoneal shunt.

REFERENCES

1. Dewan MC, Rattani A, Mekary R, et al. Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis. J Neurosurg 2018; published online April 1. DOI:10.3171/2017.10. JNS17439.
2. Kahle KT, Kulkarni AV, Limbrick DD Jr, Warf BC. Hydrocephalus in children. Lancet 2016; 387: 788–99.
3. Isaacs AM, Riva-Cambrin J, Yavin D, et al. Age-specific global epidemiology of hydrocephalus: systematic review, metanalysis and global birth surveillance. PLoS One 2018; 13: e0204926.
4. Richards HK, Seeley HM, Pickard JD. Efficacy of antibiotic-impregnated shunt catheters in reducing shunt infection: data from the United Kingdom Shunt Registry. J Neurosurg Pediatr 2009; 4: 389–93.
5. Drake JM, Kestle JR, Milner R, et al. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. Neurosurgery 1998; 43: 294–303.
6. Fernandez-Mendez R, Richards HK, Seeley HM, Pickard JD, Joannides AJ. Current epidemiology of cerebrospinal fluid shunt surgery in the UK and Ireland (2004–2013). J Neurol Neurosurg Psychiatry 2019; 90: 747–54.
7. Vinchon M, Dhellemmes P. Cerebrospinal fluid shunt infection: risk factors and long-term follow-up. Childs Nerv Syst 2006; 22: 692–97.
8. Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. Pediatr Infect Dis J 2002; 21: 632–36.
9. Thomas R, Lee S, Patole S, Rao S. Antibiotic-impregnated catheters for the prevention of CSF shunt infections: a systematic review and meta-analysis. Br J Neurosurg 2012; 26: 175–84.
10. Klimo P Jr, Thompson CJ, Ragel BT, Boop FA. Antibiotic- impregnated shunt systems versus standard shunt systems: a meta- and cost-savings analysis. J Neurosurg Pediatr 2011; 8: 600–12.
11. Jenkinson MD, Gamble C, Hartley JC, et al. The British antibiotic and silver-impregnated catheters for ventriculoperitoneal shunts multi-centre randomised controlled trial (the BASICS trial): study protocol. Trials 2014; 15: 4.
12. Kulkarni AV, Drake JM, Rabin D. An instrument to measure the health status of children with hydrocephalus: the Hydrocephalus Outcome Questionnaire. J Neurosurg 2004; 101: 134–40.
13. Pintilie M. Dealing with competing risks: testing covariates and calculating sample size. Stat Med 2002; 21: 3317–24.
14. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol 1971; 44: 793–97.
15. Fine PF, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94: 496–509.
16. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause- specific hazards and cumulative incidence functions. J Clin Epidemiol 2013; 66: 648–53.
17. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017; 36: 4391–400.
18. Curtis L. Unit costs of health and social care. 2017. https://doi.org/ 10.22024/UniKent/01.02/65559 (accessed March 10, 2019).
19. Department of Health and Social Care. NHS reference costs 2015 to 2016. https://www.gov.uk/government/publications/nhs-reference- costs-2015-to-2016 (accessed March 10, 2019).
20. NHS England. NHS national tariff payment system 2016/17. https://www.gov.uk/government/publications/nhs-national-tariff- payment-system-201617 (accessed March 10, 2019).
21. Joint Formulary Committee. British national formulary. London: BMJ Group and Pharmaceutical Press, 2017.
22. Govender ST, Nathoo N, van Dellen JR. Evaluation of an antibiotic-impregnated shunt system for the treatment of hydrocephalus. J Neurosurg 2003; 99: 831–39.
23. Keong NC, Bulters DO, Richards HK, et al. The SILVER (Silver Impregnated Line Versus EVD Randomized trial): a double-blind, prospective, randomized, controlled trial of an intervention to reduce the rate of external ventricular drain infection. Neurosurgery 2012; 71: 394–403.
24. Jamjoom AAB, Joannides AJ, Poon MT, et al. Prospective, multicentre study of external ventricular drainage-related infections in the UK and Ireland. J Neurol Neurosurg Psychiatry 2018; 89: 120–26.
25. Attenello FJ, Garces-Ambrossi GL, Zaidi HA, Sciubba DM, Jallo GI. Hospital costs associated with shunt infections in patients receiving antibiotic-impregnated shunt catheters versus standard shunt catheters. Neurosurgery 2010; 66: 284– 89.
26. Farber SH, Parker SL, Adogwa O, Rigamonti D, McGirt MJ. Cost analysis of antibiotic-impregnated catheters in the treatment of hydrocephalus in adult patients. World Neurosurg2010; 74: 528–31.
27. Parker SL, McGirt MJ, Murphy JA, Megerian JT, Stout M, Engelhart L. Cost savings associated with antibiotic- impregnated shunt catheters in the treatment of adult and pediatric hydrocephalus. World Neurosurg 2015; 83: 382–86.
28. Edwards NC, Engelhart L, Casamento EM, McGirt MJ. Cost-consequence analysis of antibiotic-impregnated shunts and external ventricular drains in hydrocephalus. J Neurosurg 2015; 122: 139–47.
29. Root BK, Barrena BG, Mackenzie TA, Bauer DF. Antibiotic impregnated external ventricular drains: meta and cost analysis. World Neurosurg 2016; 86: 306–15.