PRIFYSGOL

BANGOR

UNIVERSITY

Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multi-centre, single-blinded, randomised trial and economic evaluation

Mallucci, C.L.; Jenkinson, M.D.; Conroy, Eliabeth J.; Hartley, John C.; Brown, Michaela; Dalton, Joanne; Kearns, Tom; Moitt, Tracey; Griffiths, Michael J.; Culeddu, Giovanna; Solomon, Tom; Hughes, Dyfrig; Gamble, Carol

The Lancet

Cyswllt i'r cyhoeddiad / Link to publication

09. Oct. 2020

Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multi-centre, single-blinded, randomised trial and economic evaluation

1

* Professor Conor L Mallucci[1] FRCS

*Michael D Jenkinson[2,3] FRCS

Elizabeth J Conroy[4] MSc

John C Hartley[5] FRCPath

Michaela Brown[4] MSc

Joanne Dalton[4] BA

Tom Kearns[4]

Tracy Moitt[4]

Michael J Griffiths[6, 7] FRCP

Giovanna Culeddu[8] MSc

Professor Tom Solomon[6, 9] FRCP

Professor Dyfrig Hughes[8] PhD

Professor Carrol Gamble[4] PhD

For the BASICS study Collaborators

*Joint 1st authors

[1]Department of Paediatric Neurosurgery

Alder Hey Children's Hospital

Liverpool, UK

[2]Department of Neurosurgery

The Walton Centre NHS Foundation Trust

Liverpool, UK

[3]Institute of Translational Medicine

University of Liverpool

Liverpool, UK

[4]Clinical Trials Research Centre

University of Liverpool

Liverpool, UK

[5]Department of Microbiology

Great Ormond Street Children's Hospital

London, UK

[6]Institute of Infection and Global Health

University of Liverpool

Liverpool, UK

[7]Department of Paediatric Neurology

Alder Hey Children's Hospital

Liverpool, UK

[8]Centre for Health Economics and Medicines Evaluation

Bangor University

Bangor, UK

[9] Department of Neurology

The Walton Centre NHS Foundation Trust

Liverpool, UK

Correspondence to:

Professor Conor L Mallucci

Department of Paediatric Neurosurgery

Alder Hey Children's Hospital

Liverpool, L12 2AP, UK

cmallucci@me.com

Tel: 07710 498920

Word counts

Abstract: 303

Main text: 4490

Tables: 3

Figures: 2

Summary

Background

Insertion of a ventriculoperitoneal shunt for hydrocephalus is one of the commonest neurosurgical procedures worldwide. Shunt infection affects up to 15% of patients, resulting in long hospital admission, multiple surgeries, reduced cognition and quality of life. The aim of this trial was to determine the clinical and cost-effectiveness of antibiotic (rifampicin and clindamycin) or silver shunts compared to standard shunts at reducing infection.

Methods

Patients with hydrocephalus of any aetiology, undergoing insertion of their first ventriculoperitoneal shunt were randomised (1:1:1) to receive standard, antibiotic or silver shunts. Twenty-one neurosurgery units in the UK and Ireland participated. Primary outcome was time to shunt failure due to infection. Secondary outcomes were time to shunt removal for suspected infection, shunt failure of any cause, reason for failure (infection, mechanical), types of shunt infection, time to infection following first clean revision and cost-effectiveness. Outcomes were analyzed by intention-to-treat. [ISRCTN49474281].

Findings

Between June 26, 2013 and Oct 9, 2017, 1605 patients, from neonate to 91 years of age, were randomised to 536 standard, 538 antibiotic, and 531 silver shunts. Infection occurred in 6·0% of standard, 2·2% of antibiotic and 5·9% of silver shunts. Compared to standard, antibiotic shunts were associated with lower rates of infection (cause specific Hazard Ratio (csHR) [97.5% confidence interval]: 0·38, [0·18, 0·80], $p<0·01$) and (subdistribution Hazard Ratio, sHR 0·38 [0·18, 0·80], $p<0·01$). Silver shunts were not associated with lower rates of infection compared to standard (csHR: 0·99, [0·56, 1·74], $p<0·96$). The shunt failure rate due

to any cause was 25·0% overall and did not differ between groups. Antibiotic shunts save £135,753 per infection avoided.

Interpretation

Antibiotic ventriculoperitoneal shunts have a reduced infection rate compared to standard shunts, whereas silver shunts do not. Antibiotic shunts are cost saving.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Key words

Ventriculoperitoneal shunt, infection, clinical trial, antibiotic, silver, standard

Introduction

Hydrocephalus affects one in every five hundred births.[1] It also affects older children and adults of all ages and can be secondary to a variety of causes including haemorrhage, trauma, infection and intracranial tumours.[2] A recent systematic review and meta-analysis reported the hydrocephalus prevalence to be 88/100,000 in children, 11/100,000 in adults and 175/100,000 in the elderly.[3] The commonest treatment for hydrocephalus is the ventriculoperitoneal shunt, which comprises proximal (ventricular) and distal (peritoneal) silicone catheters joined by a valve to drain cerebrospinal fluid (CSF) from the ventricles 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, require prolonged hospitalization and antibiotics, surgery to remove the infected shunt and to place a new shunt once the infection has been treated. Shunt infection impacts on health-related quality of life, cognitive function,[7] and survival, with the number of infections being an independent predictor of death.[8]

Impregnated shunt catheters have been introduced as a means to reduce infection in addition to the usual surgical site infection prevention care bundles. 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 did not find any high quality evidence to support their comparative effectiveness at reducing shunt infection[9,10]. Consequently, practice is variable across the world, with selection based on neurosurgeon preference and costs.

We conducted the British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal shunts multi-center randomised controlled trial (BASICS) to assess the

clinical and cost-effectiveness of antibiotic and silver shunts at reducing shunt failure due to infection, compared to standard shunts in patients undergoing insertion of their first ventriculoperitoneal shunt for hydrocephalus.

Methods

Study design

In this parallel, multi-centre randomised controlled trial we compared standard, antibiotic and silver shunts in patients undergoing insertion of their first ventriculoperitoneal shunt for hydrocephalus. Trial sites were twenty-one regional adult and paediatric neurosurgery centers in the United Kingdom and Republic of Ireland (See Section 1 of the Supplementary Appendix). Ethics approval was obtained from the North West Greater Manchester research ethics committee (ref: 12/NW/0790). The trial protocol (available at www.journalslibrary.nihr.ac.uk/programmes/hta/1010430/#/) has been published previously[11] (Substantial amendments are detailed in Section 6 of the Supplementary Appendix).

Participants

To undergo randomisation in the trial, patients could be 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 on going CSF or peritoneal infection, a previous indwelling ventriculoperitoneal shunt, multi-loculated hydrocephalus requiring multiple shunts or neuro-endoscopy, known allergy to rifampicin, clindamycin or silver, or if a ventriculo-atrial or ventriculo-pleural shunt was planned. Patients gave written informed consent or assent

for minors as appropriate. Consent for adults lacking capacity was obtained from a consultee, usually the next of kin, or an independent healthcare professional, and it was later sought again from the participant once capacity was regained.

Randomisation

Patients were randomised to standard, antibiotic or silver shunts at a ratio of 1:1:1 in random permuted blocks of 3 and 6. The randomisation sequence was generated by an independent statistician, and stratified by neurosurgical unit and age group (adult or paediatric, defined according to unit practice). The randomisation was revealed in the operating theatre at the time the shunt was required using opaque tamper-proof sealed envelopes that were opened by tearing perforated edges. Due to the different colour of the shunts it was not possible to blind the neurosurgeon and operating staff. Shunt type was not recorded in the operating record and was not disclosed outside the operating room. 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 blind to the type of shunt inserted.

Procedures

Data were collected at baseline; randomisation (pre-operative assessment); randomisation (first surgery); early post-operative assessment; first routine post operative assessment; 12 weekly follow up assessments; subsequent routine post operative assessments; and, where applicable, unscheduled visits/admissions and at shunt revision/removals (see section 2 of supplementary material). All patients received prophylactic antibiotics at the time of shunt insertion as per standard neurosurgical practice. All other parameters related to surgical shunt insertion technique e.g. choice of skin preparation, hair shave or not, number and seniority of

neurosurgeon, position on operating list were recorded but not standardised and were undertaken according to each participating neurosurgery unit's practice. Patients were followed for a minimum 6 months and maximum 2 years.

Outcomes

The primary outcome was time to shunt failure due to infection as assessed by a blinded central review panel comprised of the Chief Investigator [CLM] (or delegate for participants treated by the chief investigator [MDJ]) and trial microbiologist [JCH], masked to allocations. At first shunt revision, sites recorded data on clinical presentation (e.g. temperature, headache, lethargy, meningism, conscious level, wound erythema), peripheral white blood cell count, C-reactive protein (CRP), microbiology analysis of CSF (microscopy and culture), and treatment initiated (e.g. antibiotics prescribed, shunt removed). Based on these parameters the shunt failure was classified as being due to infection or not. Shunt infections were further defined as: (1) Definite – culture positive: growth of organisms from CSF on primary culture or repeated (>1) subculture [the passage [growth identified following enrichment of cells from the primary culture to fresh medium by overnight broth incubation], with or without clinical signs of infection, and managed by shunt removal and antibiotic treatment; (2) Probable – culture uncertain: growth of organisms from CSF on one subculture only, with or without clinical signs of infection, with CSF pleocytosis and/or organisms on gram stain, and managed by shunt removal and antibiotic treatment; (3) Probable – culture negative: no organisms growth but, with or without clinical signs of infection, with CSF pleocytosis and/or organisms on gram stain, and managed by shunt removal and antibiotic treatment; (4) Possible – culture uncertain: no signs of infection, no CSF pleocytosis, no organisms seen on gram stain, growth after enrichment in one CSF sample only, and managed by shunt removal and antibiotic treatment; and (5) Shunt deep

incision infection: infection of the deep surgical wound and subcutaneous shunt without any evidence of CSF infection.

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 of any cause; reason for shunt failure (infection, mechanical [blockage of any component i.e. valve or catheters], patient [unrelated medical condition e.g. appendicitis], functional [change of valve for symptomatic over- or under-drainage of CSF e.g. fixed pressure to programmable valve] as classified by treating neurosurgeon); types of bacterial shunt infection [see table 2]; time to shunt infection following first clean revision as classified by central review; Quality of life measured using the Hydrocephalus Outcome Questionnaire[12] and health economic outcomes: incremental cost per shunt failure (any cause) averted and per quality-adjusted life (QALY) gained using the EQ-5D-3L, EQ-5D-3L (proxy) or EQ-5D-3L-Y. Data on complications and serious adverse events were collected (see protocol: www.journalslibrary.nihr.ac.uk/programmes/hta/1010430/#/).

Statistical analysis

A Trial Steering Committee, comprising a majority of independent members viewing reports blinded to treatment arm, 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 for the primary outcome used the method described by Pintilie[13] with the following assumptions: (i) failure for infection was the event of interest with all other reasons for failure a competing risk; (ii) the rate of infection was 8% in the standard shunt arm[5] and 4% in the impregnated shunt (antibiotic or silver) arms; (iii) the competing risk event rate was 30%; and (iv) 5% loss to follow-up. Based on this a total sample size of 1200 with 119 events demonstrated good statistical power (88%) with

leverage for a lower event rate. An interim analysis was planned after 50% of the total events had been observed using Haybittle-Peto.[14] Monitoring of the infection rates demonstrated the majority of events occur within one month of shunt insertion (i.e. was not exponentially distributed), and that the rates 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 of 1606 with 101 events to provide 80% power; the trial steering committee agreed. The early occurrence of events and assumption of exponential risk were managed in the Pintilie[13] assumptions by reducing the accrual and follow up rates to one month. The analysis was conducted according to a pre-specified statistical analysis plan, which was updated following review of data by a statistician blind to comparative interim reports. Outcomes were analyzed according to the intention-to-treat principle and safety analyses according to the type of shunt in situ. To adjust for the three treatment arms, a p-value of 0·025 was considered statistically significant and 97.5% confident intervals (CI) were used throughout. Outcome, with shunt failure due to infection as the event of interest, used Fine and Gray[15] 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 chi-squared test. Types of organisms cultured from CSF are presented descriptively. 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 over 65 years. Age was used in preference to and recruiting centre due to prognostic value of age group and the dependency between age group and centre prevented inclusion of both covariates. Primary outcome and safety analyses were validated by independent programming from the point of raw data

extraction. All analyses were done with SAS software version 9.4 with SAS/STAT package 14.3. The trial was registered with ISCTRN: 49474281.

Economic analysis

The economic analysis (section 5 of the Supplementary Appendix) adopted the perspective of the National Health Service in the UK to estimate the incremental cost per first shunt failure (due to any cause) averted for antibiotic, silver and standard shunts. Within-trial healthcare resource use was based on responses to questionnaires, routine hospital data via Patient Level Information and Costing Systems, and entries in case report forms. Unit costs for 2016-17 were taken from standard sources (Tables S12-S14).[18-21] Silver cost £361·62, antibiotic cost £384, and standard cost £172. In the base-case analysis, costs and outcomes incurred in the second year were discounted at a rate of 3·5%, and any missing data were multiply imputed using the method of chained equations. Total costs were analysed using linear regression with the stratifying variables, time in study, intervention group and treatment failure, as predictors. Mean outcome by intervention group was analysed in the same way, but with total cost substituting treatment failure. Sensitivity analyses considered (i) applying different discount rates (0%, 1·5% and 6% per annum for both costs and outcomes); (ii) using observed data for costs (no multiple imputation); and (iii) using a generalised linear model for analysing costs. Alternative forms of cost-effectiveness, and a cost-utility analysis relating to participants aged ≥5 years were also conducted. A stratified analysis was undertaken to estimate cost-effectiveness by age group - paediatrics, adults up to 65, and ≥65 years of age.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the

data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 26, 2013 and Oct 9, 2017, there were 1606 randomisations. One patient was erroneously randomised twice and so data from the first randomization only were used (Figure 1). Fifty-three participants subsequently withdrew from follow-up (see Figure 1), of which 24 continued to provide routinely collected data. The characteristics of the three groups were similar at baseline (Table 1, Tables S4 and S5).

1601 patients had a shunt inserted (99.8%) and 1585 received the allocated shunt (Figure 1) 98·8%, N=1605). Patients not receiving a shunt (n=4), or with an infection at insertion (n=7) were not included in the primary analysis set (Figure 1). The median follow-up time for patients assessed for primary outcome was 22 months (LQ - UQ; 10-24; min to max 0 to 24, N=1594).

398 patients had revision operations (25·0%, N=1594), with 75 being centrally classified as shunt infections (4·7%, Table 2). When compared to the standard shunt over time, the antibiotic shunt decreased the rate of shunt failure due to infection (csHR: 0·38, 97·5% CI: [0·18, 0·80], $p<·01$; Table 3). Silver was comparable to standard shunts (csHR: 0·99, 97·5% CI: [0·56, 1·74], $p=0.96$; Table 3). Figure 2 shows the cumulative incidence of failure due to infection by shunt group. The majority of centrally assessed infections were classified as definite – culture positive (53/75, 70·7%).

Of the total 398 revisions, 78 (4·9%, Table 2) were defined by the treating neurosurgeon as due to suspected infection. Antibiotic but not silver shunts were associated with a significant decrease of failure due to infection when compared to 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 95·7% (381/398) of revisions (Table S6).

Kaplan-Meier curves for time to shunt failure for any cause showed no significant difference between antibiotic or silver in comparison to standard shunts (Table 3, Figure S2). The number of shunt failures was similar between the three groups (Table 2), however the underlying reason differed when comparing standard to antibiotic shunts (p=0·02, Table S7) with fewer infections for antibiotic shunts but a higher frequency of failure due to other causes.

Staphylococcus aureus (30%) and coagulase negative staphylococci (37·5%) accounted for the majority of cultured organisms (Table S8). Culture results show a reduction in staphylococcal/gram positive infections for antibiotic shunts compared to standard and silver. All three shunt types had a similar number of gram-negative infections. The proportion of culture positive infections was lowest in antibiotic shunts (50%), (compared to 68·8% in standard and 80·6% in silver shunts). The remaining infections were classified as infection by the central review panel based on the CSF white cell counts, clinical features and blood parameters (Table 2).

Following first clean (non-infected) revision (n=323), the proportion of patients with revisions for any reason (infection and no infection) increased to 39·6% (128/323; Table S9). This rate was 25% (398/1594) in de novo shunts (Table 2). The overall infection rate was also higher within this subgroup compared to de novo shunts 6·2% (20/323, Table S9) versus 4·7% (75/1594, Table 2). There was no significant difference in time to infection following first clean revision when comparing either antibiotic or silver (Table 3) to standard shunts.

The proportion of revisions of first shunt for any cause (paediatric: 225/592, 38·0%; adults up to 65 years: 118/499, 23·6%; 65 years and over: 55/503, 10·9%, Table S10) and for infection (paediatric: 47/592, 7·9%; adults up to 65 years: 23/499, 4·6%; 65 years and over: 5/503, 1·0%, Table S10) varied by participant age group. Compared to children, over time adults up to 65 years, and adults 65 or over had a significantly lower rate of shunt failure due to infection (adults under 65 csHR: 0·55, 97·5% CI: [0·31, 0·97], p=0·02; adults 65 or over csHR: 0·12, 97·5% CI: [0·04, 0·34], p<0·01; Table 3). Figures S3 and S4 display the cumulative incidence of time to shunt failure due to infection by age group and shunt stratified by age group respectively. Schoenfeld residuals supported the assumption of proportionality used in models of for time to event outcomes.

The level of missing cost data was balanced across the three intervention groups (Table S15). Disaggregated resource use and costs are presented in Tables S16-S17. Mean total costs were £18,707 (97·5% CI: £13,888, £26,966) for standard shunts, £14,192 (97·5% CI: £12,450, £17,786) for antibiotic, and £17,385 (97·5% CI: £14,649, £22,355) for silver shunts (Table S18). Responses to EQ-5D are presented in Tables S19-S21. In the base-case analysis, the total costs relating to both silver and antibiotic shunts were less than standard. Incrementally, silver shunts saved £62,358 for each additional first shunt failure due to any reason compared with standard; and antibiotic shunts saved £638,600 per additional failure in comparison to silver (Table S22). In sensitivity analyses, the incremental cost-effectiveness ratios were stable to changes in discount rate and choice of regression modelling but, based on observed data, antibiotic dominated silver shunts, and saved £56,771 for each additional failure compared with standard shunts. Antibiotic shunts were most cost-effective in paediatrics, with mean savings of £5,312 and 0·004 fewer shunt failures (Table S23). A cost-effectiveness analysis based on the incremental cost per infection averted indicated that silver shunts

were dominated by standard, whereas antibiotic shunts were dominant, saving £4,059 per 0·030 fewer infection-related shunt failures (Table S24). There were insufficient data to formally analyse Hydrocephalus Outcome Questionnaires and results are therefore presented descriptively (Tables S25-S26). In the cost utility analysis, antibiotic shunts were dominated by silver. Compared with standard, silver shunts were £183 more costly, and yielded 0·096 additional QALYs overall, resulting in an incremental cost-effectiveness ratio of £1,904 per QALY gained, and a probability of 0.52 of being cost-effective at £20,000 per QALY (Figure S5).

There were no serious adverse events. A total 654 adverse events were reported in 413 patients (25·8%, N=1601 who received a shunt). The proportion of patients experiencing an event was highest for silver shunts (Standard: 25·4%; Antibiotic: 23·3%; Silver: 36·4%, Table S11). Common adverse events were ventricular catheter obstruction (96 events in 79 patients); shunt valve obstruction (65 events in 52 patients); and valve change for symptomatic over drainage (54 events in 50). All of these were expected events in the context of re-admission for shunt revision.

Discussion

In this trial of patients with hydrocephalus undergoing insertion of a first permanent ventriculoperitoneal shunt the infection rates were 6·0% for those receiving standard shunts, 2·2% for antibiotic shunts and 5·9% for silver shunts. Compared to standard shunts, antibiotic shunts were significantly associated with a lower rate of infection while no such effect was evident for silver shunts. 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.

The BASICS trial provides definitive evidence in the debate on use of using antibiotic or silver shunts to reduce infection. A previous randomised trial that was underpowered compared antibiotic to standard shunts, but did not show a statistically significant difference in the risk of infection (relative risk: 0·38 CI: 0·11, 1·30; p=0·12).[22] Additionally, systematic reviews and meta-analyses did not find any high quality evidence to support the comparative effectiveness of antibiotic shunts at reducing infection.[9,10] Silver catheters have only been evaluated for use in temporary external ventricular drains, not permanent implanted shunts. A randomised trial of external ventricular drains (silver versus standard) reported a reduction in infection from 21·4% (30/140) to 12·3% (17/138) (p=0·042),[23] although this is much higher than the UK national reported infection rate (9·3%).[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 are both clinically and cost effective and will inform neurosurgery practice and shunt choice for the benefit of patients.

Correctly diagnosing shunt infection when the CSF is culture positive is straightforward, however this only applies to around 70% of cases. When the CSF is culture negative the treating neurosurgeon must consider other parameters including, CSF white cell count, clinical symptoms and signs and prior treatment with antibiotics. In these circumstances removal of the shunt and antibiotic treatment often leads to resolution of the presumed infection and patient recovery. 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 68·8% in standard shunts, 50·0% in antibiotic shunts and 80·6% in silver shunts. There was a lower rate of culture positive infection with antibiotic shunts. Our analysis allowed for culture negative infections to be included when there was sufficient supporting clinical evidence of shunt infection. This was 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 in favour of antibiotic shunts when only culture positive infections were analysed. The reduction of infections seen is consistent with the expected microbiological spectrum of the antibiotic shunts, which are especially active against gram-positive organisms, and were designed to prevent *Staphylococcus* species infection. The culture results show a large reduction in staphylococcal infection compared to standard and silver shunts, which accounts for the majority of the reduction. 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 shunt failure rate was the same for all groups even though infection was reduced in antibiotic shunts. When one removes infection as a cause, the clean non-infected revision rates were slightly higher for antibiotic shunts. The cause is unclear but one hypothesis is that the antibiotic catheters may convert an 'infected' shunt revision into an apparently 'clean' shunt revision. This might occur because low virulent pathogens 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 low in number or not able to grow in the presence of the eluted antibiotics. However, changes in CSF composition and flow (such as debris or high protein) may lead to blockage of the intricate valve mechanism. Our study was not powered or designed to answer this question directly, but it will serve as a future important research question. Nevertheless, from the patient perspective, whilst mechanical shunt revision still requires surgery which may impact on their quality of life, the hospital admission is short, prolonged antibiotics are not required and patients recover more quickly with fewer long-term neurological sequelae when compared to shunt infection.[7,8]

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 within BASICS estimated that although antibiotic shunts are twice the price of standard, this upfront cost could be justified by the reduced infection rate and associated cost savings of further surgery and prolonged hospital care. Based on the primary economic outcome of incremental cost per shunt failure (due to any cause) averted, there appeared to be large potential savings for additional cases of shunt failures with silver and antibiotic compared to standard. This conservative estimate does not assume equivalence despite no difference between groups in shunt failure rates. Had a cost-minimisation analysis been considered appropriate, the saving per patient having an antibiotic rather than a standard shunt would be £4,515 (95% CI £433, £8,597). In this context, the secondary outcome based on the incremental cost per shunt infection averted is relevant. Compared with standard, silver shunts were dominated, but antibiotic shunts were dominant, saving £4,059 per 0·030 fewer infection-related failures; equating to £135,753 per infection avoided. The cost-utility analysis was limited with respect to missing data, and exclusion of participants who were at highest risk of shunt infections.

The strengths of this study are that: (i) infections were centrally classified blind to treatment allocation thereby removing the risk of bias by the treating neurosurgeon; (ii) participant retention was very high due to the nature of the intervention and the primary outcome (patients with infected shunts are always re-admitted to hospital); (iii) patient withdrawal was low (n=53, 3·3%) so it is unlikely events were missed; (iv) participants were recruited across the whole of the UK and Republic of Ireland to encompass all ages and socio-

economic classes; (v) the study samples size was large; and (vi) the results have wide generalizability because we did not mandate a specific surgical shunt insertion technique.

Some limitations of the trial should be noted. First it was not possible to blind the treating neurosurgeon to the shunt type because the physical appearance of the shunts is distinctive. Shunt type was blinded to the patient and not recorded in the patient records. The majority of 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 given the work rotas of neurosurgical staff. Furthermore, classification of shunt infection between treating neurosurgeon and central assessment had high agreement (95·7%), suggesting that any bias that the treating neurosurgeon may have had did not impact the study conclusion. Second, ventriculoatrial and ventriculopleural shunts were excluded although we postulate the results are translatable to patients undergoing these procedures. Finally, the return rate for patient reported outcomes was low limiting the analysis of the impact of shunt infection on patients, and the reliability of the cost utility analysis.

The BASICS study is the largest prospective randomised study for shunts in hydrocephalus worldwide. The study collected blood and CSF samples from participants that 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 will be analysed and used to will be analysed and used to develop recommendations and healthcare policy for patients undergoing insertion of ventriculoperitoneal shunts.

In conclusion, antibiotic shunts significantly reduce the infection rate and probability of infection compared to standard shunts in all age groups, whereas silver shunts do not. The routine use of these shunts would carry substantial costs savings. Antibiotic shunts should be the first choice for patients with hydrocephalus undergoing insertion of their first ventriculoperitoneal shunt.

Panel: Research in context

Evidence before this study

A systematic review comparing antibiotic against standard shunts identified one randomised trial, one prospective cohort study and ten retrospective studies; none were adequately powered to detect a difference in infection rates. There were no randomised trials of silver versus standard shunts. Neurosurgeons were using antibiotic and silver shunts aiming to reduce infection despite a lack of firm evidence to support this and at increased financial cost.

Added value of this study

This is the largest randomised trial for ventriculoperitoneal shunts in hydrocephalus. Antibiotic shunts significantly reduce the risk of infection compared to standard shunts in all ages. Silver shunts have the same infection rate as standard shunts. From the perspective of the NHS healthcare system antibiotic shunts save £135,753 per infection avoided.

Implications of the available evidence

From both the patient perspective and that of the treating neurosurgeon, the hospital and the health service, every effort to reduce shunt infection should be made and health technologies such as impreganted shunts with their potential to reduce such infections deserve proper evaluation through appropriately planned and powered trials. Having

demonstrated a marked reduction in such infections, with all of the potentially catastrophic and life changing health sequalae that result from each infection, the BASICS trial has provided definitive evidence to support the adoption of antibiotic shunts in all patients having their first ventriculoperitoneal shunt in the UK. The increased up-front cost of the antibiotic shunt is offset by the added health economic benefit. The benefits and implications both from an efficacy and health economic point of view are most pronounced the younger the patient. The broader, global implications of these findings require consideration of generalizability across different healthcare systems.

Contributors

Conor L Mallucci (Chief Investigator and Consultant Neurosurgeon) devised the study question and developed the study protocol in collaboration with co-investigators. He oversaw the delivery of the study, prepared study update reports, over saw clinical aspects of the statistical analysis plan and clinical interpretation of the study data. He co-led the preparation of the final report (drafting, reviewing and editing). He was Chairperson of the Trial Management Committee and member of the Central Review Panel. Joint first author.

Michael D Jenkinson (co-Chief Investigator and Consultant Neurosurgeon) devised the study question and developed the funding application and study protocol in collaboration with co-investigators. He was a member of the Trial Management Committee. He contributed to clinical interpretation of the study data and co-led the preparation of the final report (drafting, reviewing and editing). Joint first author.

Elizabeth J Conroy (Trial Statistician) contributed to protocol development and data capture methods, wrote the statistical analysis plan, undertook the final statistical analysis under the supervision of Carrol Gamble, prepared data for reports throughout

the study, prepared data tables and figures for final report, and co-led the preparation of the final report. She was a member of the Trial Management Committee.

John C Hartley (Study microbiologist) contributed to protocol development, data capture methods, central classification of infections, preparation and review of progress and final reports. He was a member of the Trial Management Committee.

Michaela Brown (Senior Statistician) contributed to protocol development and data capture methods, proposed statistical analysis methods and approved the statistical analysis plan, oversaw trial monitoring activities and was a member of the Trial Management Committee.

Tracy Moitt (Senior Trials Manager) contributed to protocol development, gave guidance and support on all aspects of governance and study delivery and supported the preparation of progress reports. She contributed to the final report (drafting and reviewer) and was a member of the Trial Management Committee.

Joanne Dalton (Data Manager) supported the Central Review Panel in their assessment and was a member of the Trial Management Committee.

Tom Kearns (Trial Co-ordinator) contributed to protocol development, all aspects of governance and study delivery and preparation of progress reports. He contributed to the final report (reviewer) and was a member of the Trial Management Committee.

Michael J Griffiths (Senior Lecturer in Paediatic Neurology), coordinated and developed the sample collection sub-study, contributed to protocol development, oversaw sample recruitment, collection and storage, contributed to the preparation of the final report (reviewing, editing). He was a member of the Trial Management Committee.

Giovanna Culeddu (Study Health Economist) contributed to protocol development and data capture methods, undertook the economic analysis under the supervision of Dyfrig Hughes, contributed to the final report (drafting) and was a member of the Trial Management Committee.

Tom Solomon (Professor of Neurology), assisted with obtaining grant funding, was a member of the Trial Management Committee, and reviewed the final report

Dyfrig Hughes (Senior Health Economist) led the economic evaluation, contributed to protocol development and data capture methods, contributed to the writing of the report (drafting, reviewing and editing) and was a member of the Trial Management Committee.

Carrol Gamble (Statistical lead) led study design, developed the funding application, study protocol and data capture methods in collaboration with co-investigators. CG led blind review of the data and supervised the final analysis. She contributed to the preparation of the final report (drafting, reviewing and editing) and was a member of the Trial Management Committee.

Data sharing agreement

Individual participant data that underlie the results reported in this article, after deidentification, will be made available. The study protocol, statistical analysis plan and consent forms will also be made available. Data will be available beginning 9 months and ending 3 years after publication. Data will be available to researchers whose proposed use of the data is approved by the original study investigators. Proposals should be directed to the corresponding authors and requestors will need to sign a data access agreement.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

References

1.   Dewan MC, Rattani A, Mekary R, et al. Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis. *J Neurosurg* 2018: 1-15.
2.   Kahle KT, Kulkarni AV, Limbrick DD, Jr., Warf BC. Hydrocephalus in children. *Lancet* 2016; **387**(10020): 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**(10): 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**(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**(2): 294-303; discussion 03-5.
6.   Fernandez-Mendez R, Richards HK, Seeley HM, Pickard JD, Joannides AJ, collaborators U. Current epidemiology of cerebrospinal fluid shunt surgery in the UK and Ireland (2004-2013). *J Neurol Neurosurg Psychiatry* 2019.
7.   Vinchon M, Dhellemmes P. Cerebrospinal fluid shunt infection: risk factors and long-term follow-up. *Childs Nerv Syst* 2006; **22**(7): 692-7.
8.   Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. *Pediatr Infect Dis J* 2002; **21**(7): 632-6.
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**(2): 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**(6): 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: Pediatrics* 2004; **101**: 134-40.
13.   Pintilie M. Dealing with competing risks: testing covariates and calculating sample size. *Stat Med* 2002; **21**(22): 3317-24.
14.   Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; **44**(526): 793-7.
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**(6): 648-53.
17.   Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017; **36**(27): 4391-400.
18.   Curtis L. Unit Costs of Health and Social Care. 2017. https://doi.org/10.22024/UniKent/01.02/65559 (accessed 10 March 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 10 March 2019.

20.   NHS England. NHS national tariff payment system 2016/17. https://www.gov.uk/government/publications/nhs-national-tariff-payment-system-201617 (accessed 10 March 2019.

21.   Joint Formulary Committee. British National Formulary (BNF). 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**(5): 831-9.

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**(2): 394-403; discussion 03-4.

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**(2): 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**(2): 284-9; discussion 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 Neurosurg* 2010; **74**(4-5): 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**(3): 382-6.

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**(1): 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.

Tables

Table 1

Baseline patient characteristics and physical examination of the intention to treat population

Baseline Characteristic	Standard shunt	Antibiotic shunt	Silver shunt	Total
Patients randomised	536	538	531	1605
Age at randomisation (years)				
N	536	538	531	1605
Med (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)
(Min, Max)	(0·0, 90·3)	(0·0, 88·9)	(0·0, 91·1)	(0·0, 91·1)
Age category, n (%)				
Paediatric	200 (37·3)	201 (37·4)	198 (37·3)	599 (37·3)
Adult (<65 years)	174 (32·5)	156 (29·0)	172 (32·4)	502 (31·3)
Adult (≥65 years)	162 (30·2)	181 (33·6)	161 (30·3)	504 (31·4)
Gender, n (%)				
Female	246 (46·0)	260 (48·3)	282 (53·1)	788 (49·1)
Male	289 (54·0)	278 (51·7)	249 (46·9)	816 (50·9)
Missing	1	0	0	1

Note: Med: Median; LQ: Lower Quartile; UQ: Upper Quartile; Min: Minimum; Max: Maximum

Table 2

Summary of revisions, and reasons for revision, of first shunt according to catheter type and assessor

	Standard shunt		Antibiotic shunt		Silver shunt		Total	
	N	%	N	%	N	%	N	%
Summary of surgeries								
Randomised	536		538		531		1605	
Eligible for primary outcome [1]	533	99·4	535	99·8	526	99·4	1594	99·6
No shunt removal/revision	403	75·6	403	75·3	390	74·1	1196	75·0
Shunt removal/revision (for any cause)	130	24·4	132	24·7	136	25·9	398	25·0

Reason for revision as classified by central review								
Reason for revision								
Revision for infection	32	6·0	12	2·2	31	5·9	75	4·7
Revision for other reason (no infection)	98	18·4	120	22·4	105	20·0	323	20·3
Type of infection								
Shunt CSF or peritoneal								

infection								
Definite – Culture positive	22	68·8	6	50·0	25	80·6	53	70·7
Probable – Culture uncertain	1	3·1	0	0·0	2	6·5	3	4·0
Probable – Culture negative	3	9·4	3	25·0	1	3·2	7	9·3
Possible – Culture uncertain	1	3·1	0	0·0	1	3·2	2	2·7
Clinically classified infection [2]	1	3·1	0	0·0	0	0·0	1	1·3
Shunt deep incisional infection								
Shunt deep incisional infection	4	12·5	3	25·0	2	6·5	9	12·0

Reason for shunt revision as classified by treating neurosurgeon								
Suspected infection	33	6·2	15	2·8	30	5·7	78	4·9
Revision for other reason (no infection)	97	18·2	117	21·9	106	20·2	320	20·1

[1] Randomised participants that did not receive a shunt (n=4) and had infection at time of insertion (n=7) were excluded from the primary outcome set, see Figure 2.

[2] Where the committee was unable to classify an infection, an infection was identified as reported on the case report forms.

There was one case where the committee was unable to classify and this was clinically classified as an infection.

Table 3: Hazard ratio estimates from multivariate regression modelling

Primary outcome									
Time to removal of the first shunt due to infection, as assessed by central review [1]	*Model estimate*		*N events*	*csHR*	*(97·5% CI)*	*P-value*	*sHR*	*(97·5% CI)*	*P-value*
	Shunt	Standard	32	-	-	-	-	-	-
		Antibiotic	12	0·38	(0·18, 0·80)	<0·01	0·38	(0·18, 0·80)	<0·01
		Silver	31	0·99	(0·56, 1·74)	0·96	0·99	(0·56, 1·72)	0·95
	Age group	Paediatric	47	-	-	-	-	-	-
		Adult (<65 years)	23	0·55	(0·31, 0·97)	0·02	0·56	(0·32, 0·99)	0·02
		Adult (≥65 years)	5	0·12	(0·04, 0·34)	<0·01	0·12	(0·04, 0·35)	<0·01

Secondary outcomes									
Time to removal of the first shunt due to suspected infection, as assessed by treating neurosurgeon [1]	*Model estimate*		*N events*	*csHR*	*(97·5% CI)*	*P-value*	*sHR*	*(97·5% CI)*	*P-value*
	Shunt	Standard	33	-	-	-	-	-	-
		Antibiotic	15	0·45	(0·23, 0·91)	0·01	0·45	(0·23, 0·91)	0·01
		Silver	30	0·93	(0·53, 1·64)	0·77	0·92	(0·53, 1·61)	0·74
	Age group	Paediatric	50	.	.	.	.	.	.
		Adult (<65 years)	23	0·51	(0·29, 0·91)	<0·01	0·53	(0·30, 0·93)	0·01
		Adult (≥65 years)	5	0·11	(0·04, 0·31)	<0·01	0·12	(0·04, 0·33)	<0·01

Time to removal/revision of the first shunt for any cause [1]	Model estimate		N events	HR	(97·5% CI)	P-value
	Shunt	Standard	130	.	.	.
		Antibiotic	132	1·01	(0·77, 1·33)	0·94
		Silver	136	1·08	(0·82, 1·42)	0·54
	Age group	Paediatric	226	.	.	.
		Adult (<65 years)	118	0·57	(0·44, 0·74)	<0·01
		Adult (≥65 years)	55	0·25	(0·18, 0·35)	<0·01

Time to failure of second shunt due to infection, following clean revision [2]	Model estimate		N events	csHR	(97·5% CI)	P-value	sHR	(97.5% CI)	P-value
	Shunt	Standard	9	-	-	-	-	-	-
		Antibiotic	6	0·55	(0·17, 1·81)	0·26	0·55	(0·17, 0·75)	0·25
		Silver	5	0·47	(0·13, 1·63)	0·17	0·48	(0·14, 1·67)	0·19
	Age group	Paediatric	10	-	-	-	-	-	-
		Adult (<65 years)	9	1·64	(0·58, 4·61)	0·28	1·72	(0·62, 4·81)	0·24
		Adult (≥65 years)	1	0·34	(0·03, 3·64)	0·14	0·37	(0·04, 3·91)	0·14

csHR: Cause-specific hazard ratios from multivariate Cox model with infection as event of interest and both shunt and age group as covariates.

sHR: Sub-distribution hazard ratios from multivariate Fine-Gray model with infection as event of interest, revision not for infection as a competing risk, and both shunt and age group as covariates.

HR: Hazard ratios from multivariate Cox model with revision/removal as event of interest and both shunt and age group as covariates.

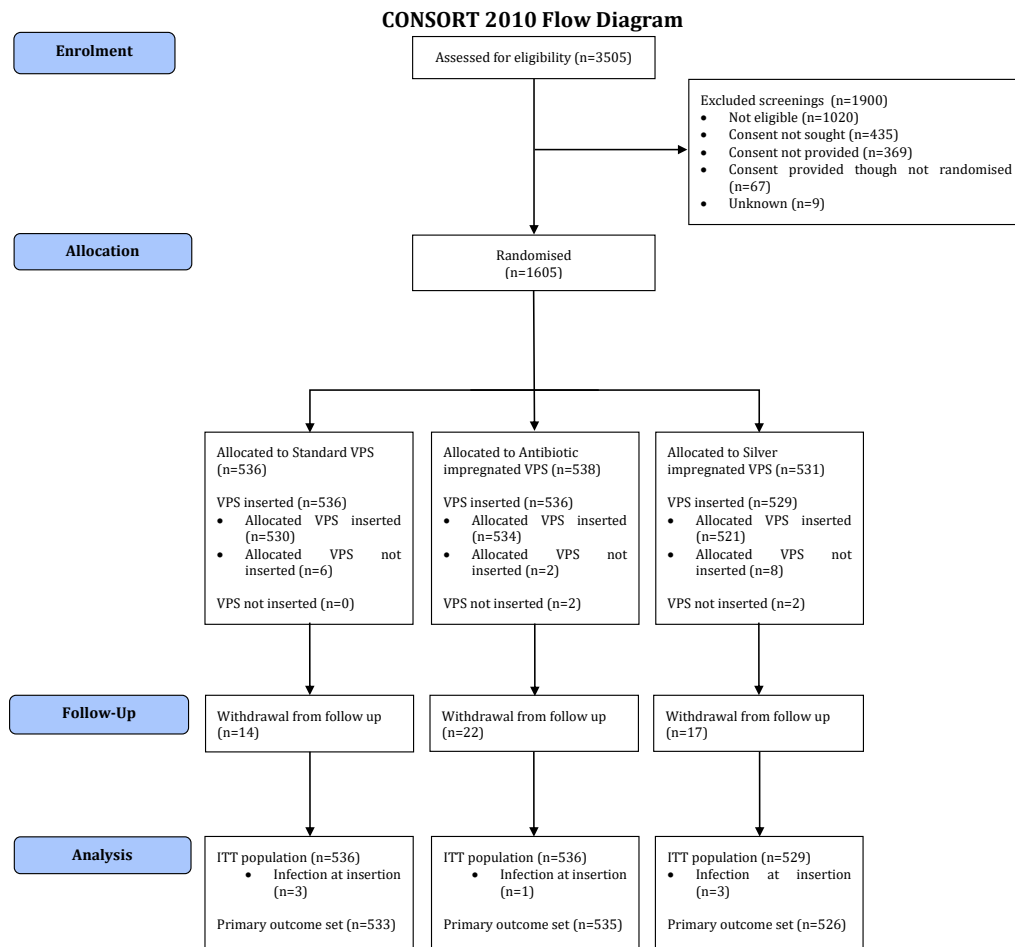Follow up time (in months) summary statistics: Median; LQ - UQ; Min to Max:

[1]Follow up time from first shunt 22; 10-24; 0 to 24.

[2]Follow up time from second shunt following clean revision: 9; 2-19; 0 to 24.

Figures

Figure 1

CONSORT 2010 Flow Diagram

CONSORT 2010 Flow Diagram

VPS: ventriculoperitoneal shunt

ITT: intention to treat

Figure 2

Cumulative incidence plots of infection (top) and competing risk (bottom) by shunt type