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A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections

Mahesh Ramanan[1,2*], Jeffrey Lipman[1,2], Andrew Shorr[3] and Aparna Shankar[4]

Abstract

Background: Ventriculostomy insertion is a common neurosurgical intervention and can be complicated by ventriculostomy-associated cerebrospinal fluid infection (VAI) which is associated with increased morbidity and mortality. This meta-analysis was aimed at determining the pooled incidence rate (number per 1000 catheter-days) of VAI.

Methods: Relevant studies were identified from MEDLINE and EMBASE and from reference searching of included studies and recent review articles on relevant topics. The Newcastle-Ottawa Scale was used to assess quality and risk of bias. A random effects model was used to pool individual study estimates and 95% confidence intervals (CI) were calculated using the exact Poisson method. Heterogeneity was assessed using the heterogeneity $\chi 2$ and I-squared tests. Subgroup analyses were performed and a funnel plot constructed to assess publication bias.

Results: There were a total of 35 studies which yielded 752 infections from 66,706 catheter-days of observation. The overall pooled incidence rate of VAI was 11.4 per 1000 catheter days (95% CI 9.3 to 13.5), for high quality studies the rate was 10.6 (95% CI 8.3 to 13) and 13.5 (95% CI 8.9 to 18.1) for low quality studies. Studies which had mean duration of EVD treatment of less than 7 days had a pooled VAI rate of 19.6 per 1000 catheter-days, those with mean duration of 7–10 days had VAI rate of 12.8 per 1000 catheter-days and those with mean duration greater than 10 days had VAI rate of 8 per 1000 catheter-days. There was significant heterogeneity for the primary outcome ($p = 0.004$, I-squared = 44%) and most subgroups. The funnel plot did not show evidence for publication bias.

Conclusions: The incidence rate of VAI is 11.4 per 1000 catheter-days. Further research should focus on analysis of risk factors for VAI and techniques for reducing the rate of VAI.

Keywords: Cerebral ventriculitis, Cerebrospinal fluid, Ventriculostomy, Catheter-related infection, Neurosurgery, Meta-analysis

Background

External ventricular drains (EVD) or ventriculostomies are commonly used in neurosurgical patients to monitor and treat raised intracranial pressure, drain intraventricular blood and temporarily treat acute hydrocephalus. Ventriculostomies are associated with a range of potential infectious and non-infectious complications [1]. Whilst rare infectious complications such as skull osteomyelitis, subdural empyema, brain abscess and distant infection are possible, the most common and clinically significant infectious complication is ventriculostomy-associated cerebrospinal fluid (CSF) infection (VAI). The VAI rate in the literature is variable, with individual studies reporting rates from 1% to 45% [2-36]. Reviews using non-meta-analytic techniques have found that 8.8% and 9.5% of patients with ventriculostomies develop VAI. VAI is associated with increased morbidity and mortality, longer intensive care unit and hospital stay, and increased healthcare costs [2,13,31].

Furthermore, there are various clinical dilemmas faced by physicians caring for patients with ventriculostomies with regard to prompt diagnosis, investigation and treatment of VAI. Clinical signs such as fever, altered consciousness, nuchal rigidity, emesis and focal neurological deficits are severely confounded by the primary neurological insult, treatments directed at preventing secondary neurological injury (sedation, neuromuscular blockade), seizures, electrolyte disturbances and non-neurological

* Correspondence: ramanan.mahesh@gmail.com
[1]Burns Trauma Critical Care Research Centre, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
[2]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Herston, Brisbane, Queensland 4029, Australia
Full list of author information is available at the end of the article

infections. CSF signs are confounded by intraventricular or subarachnoid blood, neurosurgical interventions, systemic antimicrobial therapy and antibiotic-impregnated catheters (AIC). Ventriculostomies, like other devices inserted through the skin, can become colonized by skin organisms. Colonization is not necessarily indicative of CSF infection, though CSF cultures may be positive. These difficulties are reflected in the lack of consensus definition for VAI, uncertainty regarding the trigger for empirical antibiotic therapy and the resultant wide variations in practice relating to both.

The primary aim of this systematic review and meta-analysis was to determine the pooled incidence rate of VAI. Secondary aims were to explore factors (such as duration of ventriculostomy treatment, age group, CSF infection definition, CSF culture frequency) associated with the incidence rate of VAI and to describe the microbiological findings associated with VAI. This study was conducted using the PRISMA guidelines for conduct of systematic reviews [37].

Methods

Selection criteria

All observational studies, both retrospective and prospective, that reported VAI rate were included. Randomized controlled trials of interventions were not included. When duplicate cohorts were identified, the results from the most recent publication were included to avoid overlap.

Patients with ventriculostomies were included, regardless of age or underlying diagnosis. Patients with intracranial pressure monitors or internalized CSF shunts were excluded.

Studies that reported VAI rates as infections per 1000 catheter-days and studies where this could be calculated from published data were included. We anticipated that various different definitions of VAI would be identified and all of these definitions were included.

Search methods

Relevant studies of all languages were identified from MEDLINE (1966–2013) and EMBASE (1966–2013) databases (search strategy in Table 1). The references of all included studies and relevant reviews [1,38-41] were searched for additional studies. The literature and reference search were performed by M.R. in June 2013.

Titles and abstracts were reviewed, and relevant studies were selected for full text review. Studies which met the pre-specified inclusion criteria on full text review were selected for inclusion in the meta-analysis. Reasons for exclusion were recorded. The full text review was performed by two authors (M.R. and Ap.S.) with disputes resolved by discussion.

Table 1 MEDLINE and EMBASE search strategy

1.	exp Ventriculostomy/
2.	(external adj25 ventricular).tw.
3.	(ventricular drain or ventricular catheter).tw.
4.	exp Cerebrospinal Fluid Shunts/ or exp Ventriculoperitoneal Shunt/
5.	or/1-4
6.	exp Postoperative Complications/ or exp Surgical Wound Infection/ or exp Bacterial Infections/
7.	exp Antibiotic Prophylaxis/
8.	exp Cerebral Ventriculitis/ or exp Meningitis/
9.	ventriculitis.tw.
10.	(cerebrospinal adj25 infection).tw.
11.	or/6-10
12.	5 and 10

Data collection

A data collection spreadsheet was created in Microsoft Excel 2010 and data extracted by two authors (M.R. and Ap.S.). The following data were extracted from each selected study; publication year, country, study type (retrospective or prospective), gender, mean age, numbers of patients, ventriculostomies, catheter-days and VAI's. The following data were extracted for subgroup analyses and secondary objectives; CSF culture frequency, VAI definition, underlying diagnosis, antibiotics, AIC, duration of ventriculostomy and microbiological findings.

Quality appraisal

Quality appraisal was conducted using the Newcastle-Ottawa scale (NOS) [42]. For cohort studies, the NOS is scored out of nine stars, four for selection, two for comparability and three for outcome. For this review, four of the nine items were relevant ("representativeness of the exposed cohort", "demonstration that outcome of interest not present at start of study", "assessment of outcome" and "adequacy of follow-up"). We defined studies that scored zero to two stars as low quality, and studies that scored three or four stars as high quality for sensitivity analysis purposes.

Statistical analysis

The outcome of interest was incidence rate of VAI per 1000 catheter-days. 95% confidence intervals (CI) were calculated for individual studies using an exact Poisson method in Statistical Analysis Software 9.2 (SAS, Cary, NC, USA) with PROC GENMOD. The meta-analysis was performed in Microsoft Excel 2010 [43] using the random effects method [44] to determine the pooled incidence rate. Forest plots were created to provide visual representation of the data and were inspected for heterogeneity. For objective measures of heterogeneity, the

heterogeneity χ2 and I-squared tests [45] were performed. A significance threshold of p = 0.05 was applied to the heterogeneity χ2. I-squared values less than 25% were defined as low heterogeneity, 25-50% as moderate and greater than 50% as high heterogeneity.

Pre-specified subgroup analyses were performed to test the effect of study type (retrospective versus prospective), AIC usage, infection definition, culture frequency, publication year, age group and duration of ventriculostomy insertion on the incidence rate of VAI. Sensitivity analysis was performed by examining the effect of removing small studies (defined as 1000 catheter-days or less) and low quality studies (defined as one or two stars on the Newcastle-Ottawa scale). A funnel plot [46] was examined for evidence of publication bias.

Results

Literature search

5219 studies were identified in our search (Figure 1). 3314 were in MEDLINE, 1893 in EMBASE and 12 in the reference search. Out of these, 76 were chosen for full text review from which 35 met pre-specified inclusion criteria and were included in the meta-analysis.

Study characteristics

The 35 included studies (Table 2) yielded 752 VAI's from 66,707 catheter-days. There were 6681 patients from 33 studies in which this information was available. Different definitions of VAI were used across the selected studies. The two most common definitions were positive culture in 18, the Centre for Disease Control (CDC) definition [47] in five studies. Of the remaining 12 studies, five used positive culture plus clinical or other microbiological criteria and seven used positive culture or clinical or microbiological criteria to define VAI. AIC were used in four studies (33% to 100% of patients) and were not used in 18 with AIC information unavailable in the remaining 13. Patient characteristics from individual studies are presented in Table 2.

Quality appraisal

The quality of selected studies was assessed using four items from the NOS (Table 3). 11 studies met all criteria and scored four "stars" whilst 13 scored three, eight studies scored two and three scored one star. No studies scored zero stars. 31 studies scored a star for adequacy of follow-up, 26 for representativeness of the cohort, 24 for assessment of outcome and 21 for demonstration that VAI was not present at the outset.

Main results

Incidence

The 95% CI's for the individual study estimates are shown on the forest plot (Figure 2). The pooled VAI rate (Figure 2) was 11.4/1000 catheter-days (95% CI 9.3 to 13.5). Significant heterogeneity was detected using the heterogeneity χ2 test (χ2 = 60.19, degrees of freedom (df) = 34, p = 0.004). The I-squared test (I-squared = 45%) was consistent with moderate heterogeneity.

Microbiology

There were a total of 523 positive cultures from 25 studies which presented microbiological data (Figure 3). 333(64%) of these were gram positive bacteria, 177(35%) gram negative bacteria and 6(1%) were *Candida* spp., 95 were *Staphylococcus epidermidis*, with another 105 reported as

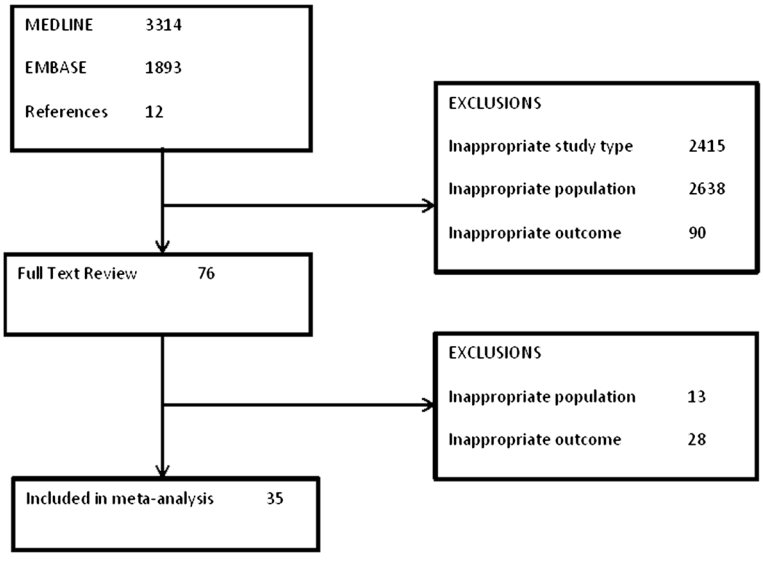

Figure 1 Flow diagram of the search strategy and exclusions at each stage.

Table 2 Characteristics of included studies

Study	Year	Country	Study Type	n (patients)	n (evd's)	Length of treatment (mean no. days)	Age (mean)	Males (%)	Trauma (%)
Alleyne [31]	2000	USA	Retrospective	308	-	9.3	46.6	50.6	27.9
Arabi [36]	2005	Saudi Arabia	Retrospective	84	99	7	34	78.6	63.1
Bota [35]	2005	Belgium	Retrospective	638	-	9.5	41.3	56.9	23
Camacho [8]	2011	Brazil	Prospective	119	130	7.1	44.4	48.7	26.9
Chi [24]	2009	Taiwan	Retrospective	155	197	18.8	58.1	63.2	-
Dasic [10]	2006	UK	Retrospective	95	113	10.7	54.7	62.1	-
Fichtner [28]	2010	Germany	Retrospective	164	-	10	53.5	50	-
Hader [17]	2000	Canada	Retrospective	157	160	5.6	8	0	40.8
Hoefnagel [2]	2008	Netherlands	Retrospective	228	-	8.1	58	49.6	3.5
Holloway [25]	1996	USA	Retrospective	584	866	7.5	29.9	77.2	100
Khalil [9]	2005	UK	Retrospective	.	24	12.3	-	-	-
Kim [34]	2012	USA	Retrospective	343	-	12.4	53.7	42	-
Kitchen [6]	2011	UK	Retrospective	133	195	7.1	55	35.3	-
Lemcke [20]	2012	Germany	Retrospective	95	95	13.7	53.6	53.7	10.5
Leverstein Van-Dall [21]	2010	Netherlands	Retrospective + Prospective	.	363	9.2	-	-	-
Lo [18]	2007	Australia	Retrospective	199	269	8.2	41	64	74
Lundberg [16]	2000	Sweden	Prospective	157	157	7.4	-	-	24.8
Lwin [27]	2012	Singapore	Retrospective + Prospective	234	-	7.8	-	65	-
Lyke [13]	2001	USA	Retrospective	157	196	5.3	54.5	42.7	0
Mahe [7]	1995	France	Retrospective	53	64	14.6	47.3	-	-
McLaughlin [19]	2012	USA	Retrospective	75	97	13.7	59	34.7	0
Moon [12]	2007	Korea	Retrospective	112	174	8.3	48.5	63.4	63.4
Park [29]	2004	USA	Retrospective	595	770	8.6	51.3	51.3	12.6
Rafiq [15]	2011	Pakistan	Retrospective	76	-	11.4	37.9	53.9	-
Rivero-Garvia [26]	2011	Spain	Retrospective	534	648	10.2	-	-	-
Roitberg [30]	2001	USA	Retrospective	103	-	10.7	-	39.8	2.9
Scheithauer [23]	2009	Germany	Prospective	225	-	11.2	-	-	-
Scheithauer [22]	2010	Germany	Prospective	158	-	14.3	-	-	-
Schodel [32]	2012	Germany	Retrospective	166	-	17.1	58.7	44	9
Schultz [11]	1993	USA	Prospective	78	94	11.9	48.8	53.8	37.2
Sloffer [33]	2005	USA	Retrospective	100	113	11.4	55.6	39	8
Smigoc [5]	2012	Slovenia	Retrospective	48	-	9.8	-	-	-
Smith [4]	1976	USA	Retrospective	56	65	4	-	-	-
Williams [14]	2011	Australia	Retrospective + Prospective	382	-	5.4	46.1	60.2	32.2
Wyler [3]	1972	USA	Retrospective	70	102	5	7.2	-	0

Table 2 Characteristics of included studies *(Continued)*

Cerebrovascular (%)	Other indications (%)	Antibiotic-impregnated catheters (%)	Periprocedural[a] antibiotics (%)	Prophylactic[b] antibiotics (%)	Culture frequency	Infection definition
50.3	21.8	0	100	67.9	twice weekly	culture
21.4	15.5	-	59.6	-	when indicated	culture or wcc[c] + glucose + clinical signs
62.2	14.7	0	100	-	daily	culture + csf[d] + clinical
53.8	19.3	0	73.1	-	when indicated	unclear
-	-	-	100	-	when indicated	culture
-	-	0	-	-	unclear	culture
56.1	-	0	67.7	0	thrice weekly	culture
7.6	51.6	0	100	43	daily	culture + gram stain or multiple cultures
78.1	18.4	0	35.5	-	thrice weekly	culture
0	0	-	-	-	when indicated	culture or wcc or csf glucose
-	-	-	-	-	unclear	culture
71	-	0	100	0	when indicated	culture
-	-	0	-	-	unclear	culture
83.2	6.3	32.6	100	0	tenth daily	culture
-	-	-	-	-	unclear	cdc definition
26	0	0	-	-	thrice weekly	cdc definition
51	24.2	0	-	-	when indicated or at removal	culture
-	-	0	-	-	when indicated	culture
0	100		100	100	when indicated	culture + wcc or glucose for low virulence organisms
-	-	-	-	-	daily	culture or wcc
100	0	100	-	-	when indicated	cdc definition
26.8	9.8	-	100	100	daily	culture + fever
66.7	20.7	-	100	100	when indicated	culture
-	-	0	100	100	when indicated	culture
-	-	42.8	-	-	when indicated	unclear
85.4	11.7	-	-	-	daily	clinical + wcc
-	-	0	0	0	when indicated	cdc definition
-	-	0	0	0	thrice weekly	cdc definition
86.1	4.8	0	100	0	unclear	culture + clinical signs
-	-	0	-	94.9	unclear	culture
72	20	100	100	-	when indicated	culture
27.1	-	-	-	-	unclear	culture or clinical signs
-	-	0	95.4	95.4	unclear	culture
38	29.8		-	-	daily retro, third daily pros	culture
4.3	95.7	0	-	62.9	insertion, withdrawal and when indicated	culture

[a]Periprocedural = antibiotic administered immediately prior to procedure.
[b]Prophylactic = antibiotic administered for 24 hours or more after the procedure.
[c]wcc = white cell count.
[d]csf = cerebrospinal fluid.

Table 3 Quality appraisal of included studies using Newcastle-Ottawa Scale

Study (Author-Date)	Representativeness	Demonstration that outcome not present at outset	Assessment of outcome (proven infection vs suspected infection based on other criteria)	Adequacy of follow-up (<5% loss)
Alleyne 2000 [31]	*	*	*	*
Arabi 2005 [36]	*			*
Bota 2005 [35]	*	*	*	*
Camacho 2011 [8]	*	*		*
Chi 2009 [24]	*	*	*	*
Dasic 2006 [10]	*		*	*
Fichtner 2010 [28]		*	*	
Hader 2000 [17]	*	*	*	*
Hoefnagel 2008 [2]	*	*	*	
Holloway 1996 [25]				*
Khalil 2005 [9]	*	*	*	*
Kim 2012 [34]	*	*	*	*
Kitchen 2011 [6]			*	*
Lemcke 2012 [20]	*	*	*	*
Leverstein Van-Dall 2010 [21]	*			*
Lo 2007 [18]	*	*		*
Lundberg 2000 [16]		*	*	
Lwin 2012 [27]	*		*	*
Lyke 2001 [13]	*	*	*	*
Mahe 1995 [7]	*			*
McLaughlin 2012 [19]				*
Moon 2007 [12]	*		*	*
Park 2004 [29]	*	*	*	*
Rafiq 2011 [15]	*	*	*	*
Rivero-Garvia 2011 [26]	*			*
Roitberg 2001 [30]				*
Scheithauer 2009 [23]	*	*		*
Scheithauer 2010 [22]	*	*		*
Schodel 2012 [32]	*		*	*
Schultz 1993 [11]		*	*	*
Sloffer 2005 [33]		*	*	*
Smigoc 2012 [5]		*	*	*
Smith 1976 [4]	*		*	
Williams 2011 [14]	*	*	*	*
Wyler 1972 [3]	*		*	*

*Denotes that the quality criteria has been met.

coagulase negative staphylococci and 77 *Staphylococcus aureus*(of which 12 were methicillin-resistant). Amongst the gram negative bacteria, *Acinetobacter* spp.(48) were the most common, followed by *Pseudomonas* spp.(31) and *Enterobacter* spp.(29). In studies without AIC, 41% (175/425) of positive cultures were gram negative bacteria whereas in studies with AIC, 10% (9/83) were gram negative bacteria.

Sensitivity analysis

Sensitivity analyses (Table 4) were performed using NOS and sample size criteria. Including only studies with

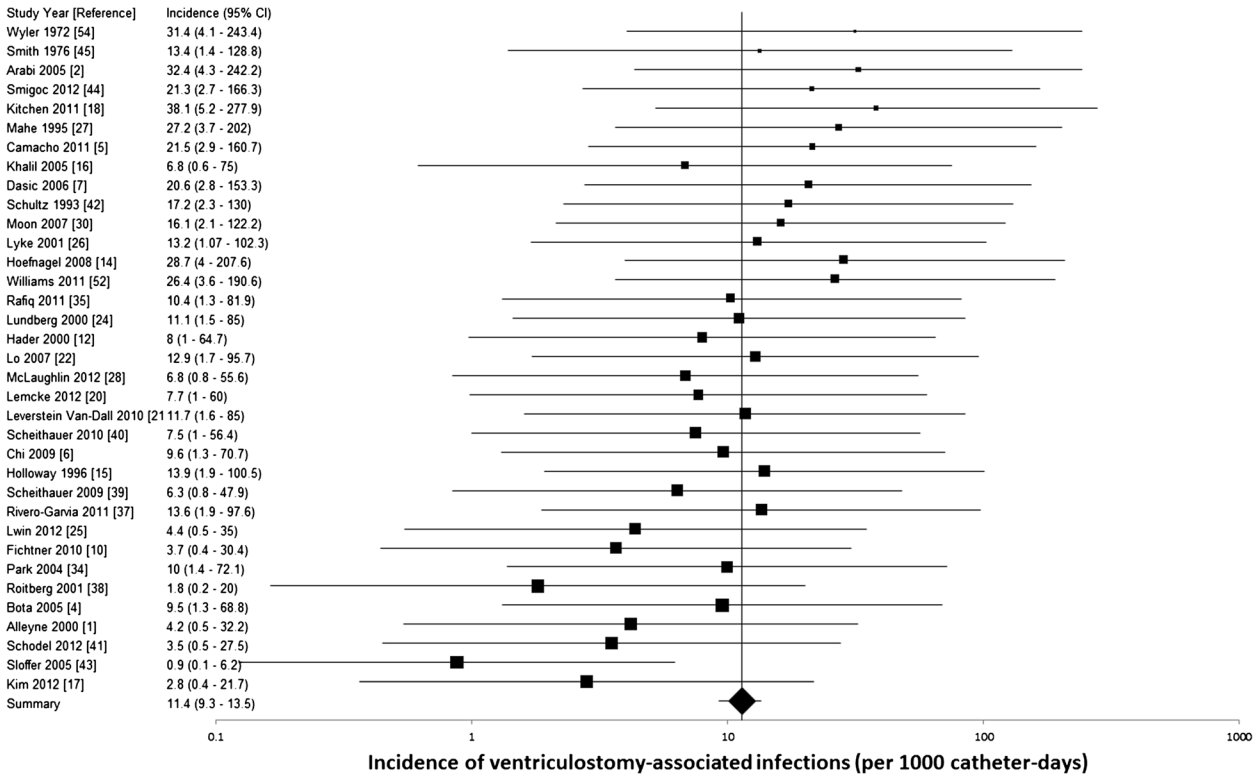

Figure 2 Forest plot of meta-analysis (random effects model) of ventriculostomy-associated infections. CI confidence interval.

NOS scores of 3 and 4, the pooled VAI rate was 10.6/1000 catheter-days (95% CI 8.3 to 13) with significant heterogeneity (p = 0.019, I-squared = 41%). The rate was 13.5/1000 catheter-days (95% CI 8.9 to 18.1, heterogeneity p = 0.046, I-squared = 46%) when studies with NOS scores of 1 and 2 only were included. With studies having sample sizes 1000 catheter-days and under, the VAI rate was 18.3/1000 catheter-days (95% CI 13.4 to 23.3) with low, insignificant heterogeneity (p = 0.34, I-squared = 11%). The rate was 9/1000 catheter-days (95% CI 6.8 to

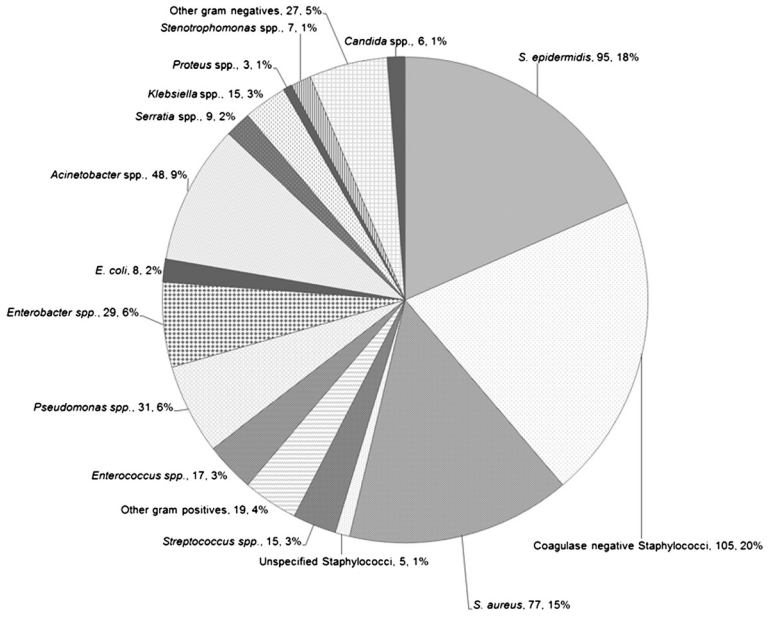

Figure 3 Pie diagram of breakdown of 523 positive cerebrospinal fluid cultures.

Table 4 Subgroup and sensitivity analyses

Comparison	n	Infections/1000 catheter-days	Lower 95% CI[a]	Upper 95% CI	p	I-squared (%)
Overall	35	11.4	9.3	13.5	0.004	44
Subgroups						
Culture frequency						
Daily culture	5	10.8	4.8	16.8	0.16	39
Culture when indicated	15	11.2	8.6	13.9	0.16	27
Other culture regimes	15	13.5	9.6	17.4	0.048	41
Infection definition						
Culture proven infection	18	11.5	8.4	14.6	0.004	54
CDC definition of infection	5	8.8	6.3	11.3	0.403	0.50
Culture plus other features	5	9.1	4.8	13.4	0.436	0
Culture or other features	7	17	10	24.1	0.347	11
Age group						
Paediatric	3	10.6	6.1	15.2	0.429	0
Adult	32	11.5	9.3	13.7	0.002	48
Year						
Publication year <2000	5	18.3	12.4	24.3	0.39	3
Publication year 2000+	30	10.5	8.4	12.6	0.002	47
Duration						
Mean duration <7 days	6	19.6	10	24.1	0.6	0
Mean duration 7-10 days	14	12.8	9.5	16	0.03	49
Mean duration >10 days	15	8	5.4	10.5	0.106	37
Study type						
Prospective	5	11	6.6	15.4	0.23	29
Retrospective	30	11.4	9.1	13.8	0.003	47
AIC						
No AIC	18	10.8	8.1	13.6	0.001	57
Unclear	13	13.7	9.8	17.6	0.19	25
AIC used	4	7.2	2.6	14.1	0.64	0
Sensitivity Analysis						
Study size						
<=1000 catheter-days	13	18.3	13.4	23.3	0.34	11
>1000 catheter-days	22	9	6.8	11.2	0.027	40
Newcastle-Ottawa score						
1 and 2	11	13.5	8.9	18.1	0.046	46
3 and 4	24	10.6	8.3	13	0.019	41

[a]CI = confidence interval.

11.2) when studies with sample size greater than 1000 catheter-days were analyzed. Heterogeneity remained significant (p = 0.027, I-squared = 40%).

Subgroup analyses

Subgroup analyses (Table 4) were performed based on age group, publication year, infection definition, study type, AIC, duration of ventriculostomy insertion and CSF culture frequency. The studies which defined VAI as positive CSF culture had a pooled VAI rate of 11.5/1000 catheter-days, those which used the CDC definition had a rate of 8.8/1000 catheter-days, those which used positive culture plus other clinical or microbiological features had a rate of 9.1/1000 catheter-days and those which used positive culture or other clinical or microbiological features had a rate of 17/1000 catheter-days. Studies which had mean duration of EVD treatment of less than 7 days had a pooled VAI rate of 19.6/1000

catheter-days, those with mean duration of 7–10 days had VAI rate of 12.8/1000 catheter-days and those with mean duration greater than 10 days had VAI rate of 8/1000 catheter-days. Studies in which AIC were used had a VAI rate of 7.2/1000 catheter-days whilst the remaining studies had a pooled rate of 12.1/1000 catheter-days. Studies published earlier than 2000 had a higher VAI rate of 18.3/1000 catheter-days compared to 10.5/1000 catheter-days for studies published 2000 or thereafter. Prospective and retrospective studies had similar VAI rates of 11 and 11.4/1000 catheter-days respectively.

Funnel plot

A funnel plot was created by plotting catheter-days versus VAI rate (Figure 4) and visually inspected for evidence of publication bias. The funnel plot revealed an excess of smaller studies with extreme estimates, both high and low, of VAI rate. There was a paucity of larger studies with extreme estimates of VAI rate. Both observations were consistent with low likelihood of publication bias.

Discussion

This meta-analysis of 35 observational studies has calculated a pooled incidence rate of VAI of 11.4/1000 catheter-days (95% CI 9.3-13.5). This translates to 1 VAI per 88 catheter-days. This result is a benchmark against which local practices can be compared. There was, however, significant heterogeneity for the pooled result ($p = 0.004$, I-squared = 44%) and most subgroup analyses. The reasons for this heterogeneity are numerous and include variations in definition of VAI, antibiotic usage, CSF investigation regimes, patient population, publication year, duration of ventriculostomy insertion, type of catheter, length of subcutaneous tunnel and potentially other unknown factors that cannot be addressed in this meta-analysis.

In comparison to previous studies [34,38] which simply added and averaged percentages to generate an overall estimate of VAI rate, we have performed, to our knowledge, the first systematic review using validated meta-analytic techniques to determine the pooled VAI rate from all published studies. The VAI rate of 11.4/1000 catheter-days can be used by individual institutions as a benchmark for comparison with their local VAI rates. The effect of interventions and changes to local practice can be quantified and compared using this rate. It can be used by future individual studies or meta-analyses of interventions aimed at reducing VAI rate to calculate numbers needed to treat. Further applications would include health economic calculations of the cost of VAI and the quantification of benefits of reducing the VAI rate [48].

From the 25 studies which reported microbiological data from 523 positive cultures, 64% of culture positive infections were caused by gram positive bacteria, predominantly coagulase negative staphylococci (39%, including *S. epidermidis*) and *S. aureus*(15%). A minority of infections (1%) were caused by *Candida* spp., and the rest (35%) by gram negative bacteria including *Acinetobacter* spp.(9.3%) and *Pseudomonas* spp.(6%) followed by enteric organisms. Traditional thinking is that skin flora, predominantly staphylococcal species, which gain entry to the subarachnoid or intraventricular space through the ventriculostomy tract cause VAI. Prophylactic and empirical antibiotics are frequently selected on this basis. Further research is required to differentiate between risk factors for gram positive and gram negative VAI, however, our findings suggest that empirical antibiotic regimes that are not active against gram negative bacteria will be inadequate in about a third of all VAI cases. Furthermore, *Acinetobacter* and *Pseudomonas* species, which are resistant to a broader range of antibiotics than the enteric gram negatives, were the most common gram negative bacteria.

Smaller studies (<1000 catheter-days) reported a much higher incidence rate of VAI (18.3/1000 catheter-days) than larger (>1000 catheter-days) studies (9/1000 catheter-days). This suggests that sampling error may have biased

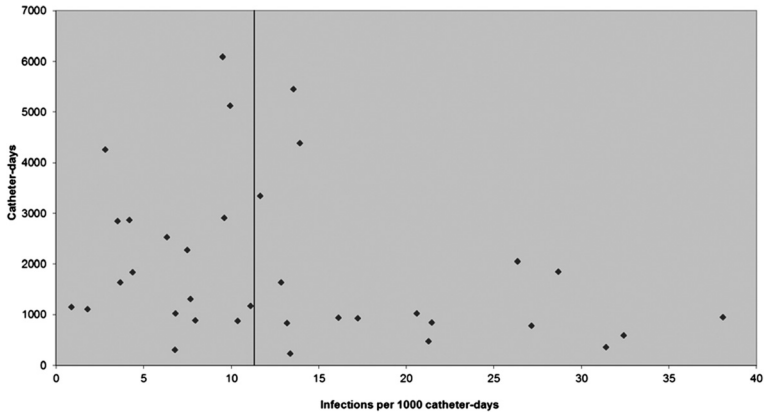

Figure 4 Funnel plot of incidence of ventriculostomy-associated cerebrospinal fluid infection versus catheter-days.

the overall result and the estimate from the larger studies may be more reflective of the true VAI rate. Subgroup analyses revealed similar VAI rates when studies were grouped according to age and culture regime. Some individual studies have suggested that frequent manipulation of ventriculostomies is a risk factor for VAI [2,49]. Our results, however, show very similar rates of VAI (10.8 and 11.2/1000 catheter-days) when comparing studies that performed daily CSF cultures with clinically indicated CSF cultures. An explanation for this is that ventriculostomies are accessed for reasons other than CSF cultures such as flushing the system when blocked with blood clots, other diagnostic tests (biochemical, cytological, immunological) and administering intrathecal medications.

Studies published prior to 2000 had a higher VAI rate (18.3/1000 catheter-days) compared to those published 2000 and thereafter (10.5/1000 catheter-days). This may be a reflection of the evolution and improvement in infection control and prevention practices over time.

The use of AIC for prevention of VAI is controversial. Whilst various analyses [40,41] have suggested a protective effect, the findings presented by Stevens et al. [50] have raised doubt as to whether the incidence of VAI is truly reduced or whether the false negative rate is increased by AIC. Our results show that studies in which AIC were utilized had a pooled VAI rate of 7.2/1000 catheter-days, considerably lower than 12.1/1000 catheter-days in studies in which AIC were not used or AIC usage was unclear. The latter rate is perhaps closer to the true rate of VAI with confounding by AIC usage removed.

There is no universally accepted definition of VAI, as evidenced by the various definitions encountered during this meta-analysis. 18 out of 35 studies defined VAI as micro-organism growth on CSF culture, and the pooled VAI rate amongst these was 11.5/1000 catheter-days. Those that used the CDC definition [47], with or without minor modifications, had a rate of 8.8/1000 catheter-days, whilst those that defined infection as positive culture plus clinical or CSF criteria also had a similar pooled VAI rate of 9.1/1000 catheter-days. Unsurprisingly, studies with a broader definition of infection, including positive culture or clinical features of meningo-ventriculitis, or abnormal CSF parameters, had a much higher rate of 17/1000 catheter-days. Strict definitions that insist upon positive CSF culture may miss some VAI when AIC are used as AIC reduce the chance of a positive culture [50]. Failure to process CSF in anaerobic media with prolonged incubation is another cause of negative cultures.

The effect of duration of ventricular catheterization on VAI rate is controversial [1]. Some institutions practice mandatory ventriculostomy revision after a certain duration [25], though mandatory revisions have not been shown to reduce VAI rate [18]. The evidence for increased duration causing an increased risk of VAI is conflicting with some studies suggesting an increasing risk with duration [3,11,13,25,51,52] longer than 5–7 days, with others showing no association [4,53-56]. In our analysis, we found decreasing VAI rate with increasing mean duration of ventricular catheterization when the studies were grouped according to duration less than 7 days, 7–10 days and greater than 10 days. The estimates were 19.6, 12.8 and 8 per 1000 catheter-days respectively. Whilst this is an unadjusted analysis that does not control for confounders, duration of treatment being a risk factor for VAI cannot be supported based on this data. Further, presence or suspicion of VAI will lead to removal and replacement of the ventricular catheter, whereas a non-infected catheter will tend to be left in situ as long as clinically indicated. Therefore, to some extent, it can be expected that the VAI rate will be higher amongst catheters with a shorter duration.

The main strengths of this meta-analysis are thorough literature search(including non-English articles) to identify all relevant published material, large number of included studies, large number of catheter-days of observation and infections and low likelihood of publication bias as detected by the funnel plot. The overall quality of studies, as assessed by the NOS, was high. Whilst efforts were made to locate all relevant published studies, unpublished data were not sought. It is plausible that this may have a significant impact on the pooled estimate of VAI rate. It is commonplace for institutions to audit their hospital-acquired infection rates. It is possible that such datasets exist in unpublished documents. This meta-analysis was also limited by reporting of VAI in formats that were not convertible to rate per 1000 catheter-days. Most of these studies expressed VAI as percentage of patients or ventriculostomies. Some causes of heterogeneity were explored in the subgroup analyses, however in this study, being a meta-analysis of cohort studies we were limited by the data that individual studies published.

Future research should focus on addressing the limitations of this meta-analysis, particularly on sourcing unpublished data from around the world, to assess the impact of this data on the results of our study. Data reporting in such a format that allows calculation of rate of events per person-time at risk should be encouraged as a standard format that allows comparisons across cohorts and pooling in meta-analyses. Participation in multicenter ventriculostomy registries should be encouraged as this will facilitate larger sample sizes, standardized data collection, exploration of heterogeneity, increased collaboration between researchers and individual patient data meta-analysis. A large, prospective observational or population study is required to confirm the results and explore the reasons for heterogeneity presented in this review. Further analyses of risk factors, as well as

identification of preventative measures for VAI could be addressed in such a study.

Conclusion

Ventriculostomies are common neurosurgical interventions frequently complicated by CSF infection. This meta-analysis has found that the VAI rate is 11.4/1000 catheter-days, or 12.1/1000 catheter-days with AIC removed. The rates across different age groups, study types, CSF culture regimes and common VAI definitions were similar, whilst being lower amongst studies with longer mean duration of ventriculostomy treatment and with AIC usage. The majority of positive cultures were gram positive bacteria, but 35% of positive cultures were gram negatives, the most common being *Acinetobacter* and *Pseudomonas* species, with subsequent implications for empirical antibiotic therapy. Future directions include more rigorous analysis of risk factors for VAI and confirmation of these data with large prospective, observational studies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MR participated in the design of the study, drafted the protocol, performed the literature search, quality appraisal and statistical analysis, and drafted the manuscript. JL conceived the design of the study, provided overall supervision and helped revise the manuscript. AS participated in the design of the study and helped revise the manuscript. ApS assisted in the full text article review and quality appraisal. All authors have approved the manuscript for submission.

Author details

[1]Burns Trauma Critical Care Research Centre, School of Medicine, University of Queensland, Brisbane, Queensland, Australia. [2]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Herston, Brisbane, Queensland 4029, Australia. [3]Medical Intensive Care Unit, Washington Hospital Center, Washington, DC, USA. [4]Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India.

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