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Review Article

Intracerebroventricular Delivery as a Safe, Long-Term Route of Drug Administration

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ABSTRACT

Intrathecal delivery methods have been used for many decades to treat a broad range of central nervous system disorders. A literature review demonstrated that intracerebroventricular route is an established and well-tolerated method for prolonged central nervous system drug delivery in pediatric and adult populations. Intracerebroventricular devices were present in patients from one to 7156 days. The number of punctures per device ranged from 2 to 280. Noninfectious complication rates per patient (range, 1.0% to 33.0%) were similar to infectious complication rates (0.0% to 27.0%). Clinician experience and training and the use of strict aseptic techniques have been shown to reduce the frequency of complications.

Keywords: intracerebroventricular, ICV, intrathecal, drug delivery, Ommaya reservoir, Rickham reservoir, complications, infections
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Introduction

Intrathecal delivery methods enable the administration of soluble therapeutics directly into the central nervous system (CNS). As an intrathecal delivery method, the intracerebroventricular (ICV) route of administration instills therapy into the cerebral ventricles via an ICV port implanted under the scalp. This route of administration, also referred to as intraventricular administration, has been used for several decades to provide treatments for pediatric and adult patients who suffer from a broad range of diseases, including infectious meningitis, intractable pain, and various types of cancer.[1-5] In addition to the ICV route, intrathecal delivery methods include single or repeated intrathecal lumbar (IT-L) injections, in which agents are directly administered into the cerebrospinal fluid (CSF) by puncturing the membranes surrounding the spinal cord (Fig 1). Intrathecal routes of administration allow therapies to bypass the blood–brain barrier (BBB) and are commonly used to treat a variety of diseases in pediatric and adult patients.[4,7-10]

As part of the neurovascular unit, the BBB is composed of tight endothelial junctions that are surrounded by a basal membrane that separates the endothelium from pericytes, astrocytes, and neurons.[7] This physiological barrier restricts the movement of large molecules between the blood, CSF, and interstitial fluid of the brain.[7,11,12] Direct delivery into the CNS is required in many circumstances when, due to the selectivity of the BBB, systemically administered therapies may fail to reach therapeutic levels in the CNS.[4,13] In some cases, intravenous therapy may be augmented or even

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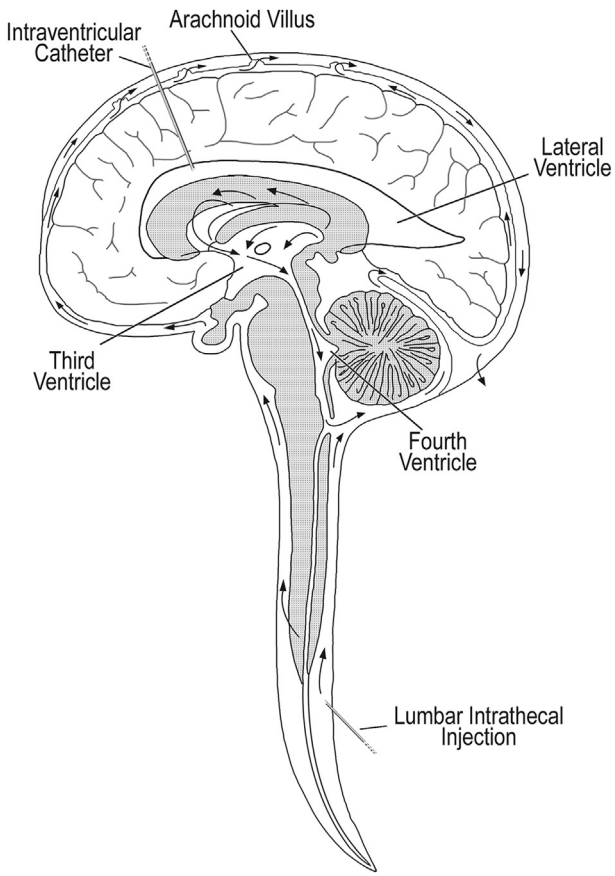

FIGURE 1.
Illustration of cerebrospinal fluid flow and typical placement of intracerebroventricular (intraventricular) and intrathecal lumbar catheters.[6] This image was adapted with permission and published in *Annals of Pharmacotherapy*, Vol. 27, Luer MS, Hatton J, Vancomycin administration into the cerebrospinal fluid: a review, 912-921, Copyright SAGE Publications (1993).

replaced with delivery systems that target the CNS to provide safe and effective doses of therapy to the CNS while minimizing systemic toxicity.[9,14,15]

To circumvent the selectivity of the BBB, therapies can be administered via ICV devices directly into the CSF.[16-18] An ICV device (e.g., Ommaya reservoir or Rickham reservoir) consists of a port that is implanted by neurosurgeons in the subgaleal space under the scalp and connected to the ventricles within the brain via an outlet catheter.[19] Drug administration via an ICV device provides greater convenience and comfort for patients compared with repeated IT-L punctures.[20,21] However, the potential for increased intracranial pressure remains a theoretical concern during administration of medications via the ICV route, especially when larger volumes are administered over a short period of time.[21] To address this concern, many studies have included the use of isovolumetric injection, noting that withdrawal of CSF before administration of the medication can help to avoid volume overload.[22-25] In addition, ICV infusion can deliver therapies in the long term and at a constant rate that does not result in increased intracranial pressure.[21,26] Once the devices are no longer therapeutically needed, they can be explanted, although oncologists routinely recommend that, in the absence of complications, these devices remain in place indefinitely.[27-29]

The distribution of intrathecally administered therapies throughout the CNS has been investigated in a number of recent publications.[4,19,22,24,26,30-35] Although one review hypothesized that the low rate of interstitial fluid secretion by microvessels of the brain can work against drug diffusion into brain tissue, and that the ICV delivery route may be a suitable strategy only for areas close to the ventricles,[19] many studies have demonstrated that ICV and IT-L administered therapies can be distributed throughout the brain and other regions of the CNS.[4,22,24,26,30-35]

Successful early stage studies of ICV-delivered therapies for new therapeutic indications (beyond oncology and pain)[24,26,30-32,34,36,37] have led to several clinical trials. These trials include recombinant human tripeptidyl-peptidase 1 administered to patients aged three to 16 years with late-infantile neuronal ceroid lipofuscinosis type 2 disease[38]; recombinant human heparan-N-sulfatase administered to patients aged 12 to 48 months with mucopolysaccharidosis IIIA[39]; and recombinant human iduronate-2-sulfatase administered to patients aged three to 18 years with mucopolysaccharidosis II.[40] In addition, at least 2 other clinical trials have used ICV devices to administer therapy: a vascular endothelial growth factor assessed in patients aged 18 to 75 years with amyotrophic lateral sclerosis[41] and a product containing platelet-derived growth factor in patients with Parkinson disease aged 30 to 75 years.[42]

The ICV route of administration is an established and globally used method of drug delivery; individual clinics' procedures and recommended guidelines on the use of ICV access devices (e.g., Ommaya and Rickham reservoirs) have been published (summarized in Fig 2).[27,43,44] Numerous studies have demonstrated that employing strict aseptic techniques when accessing ICV devices can dramatically reduce infectious complication rates,[27,44-47] and following best practices for ICV device use can prevent infectious and noninfectious complications.

The increased use of chronic ICV delivery warrants an analysis of the long-term safety and tolerability of the ICV route in both pediatric and adult patients. Because the placement of ICV devices uses common neurosurgical techniques,[48] this literature analysis does not include device implantation; rather, this review examines long-term management of the ICV access point, the duration of safe ICV device use, and the nature and rate of complications (infectious and noninfectious) associated with the ICV administration of therapies targeting the CNS.

Methods

A literature search was conducted using Embase, Scopus, and PubMed to identify articles and conference abstracts published through October 17, 2014, that included ICV as a route of administration across a range of disease states. Similar search strategies and terms were used within each database. Published articles and abstracts were searched using the following keywords: ("intracerebroventricular" or "ventricular" or "intraventricular" with "infusion" or "injection" or "drug" or "therapy" or "treatment" or "delivery") AND ("intrathecal" or "pump" or "ommaya" or "reservoir" or "rickham" or "mccomb" or "salmon" or "siphonguard" or "port" or "catheter" or "brain" or

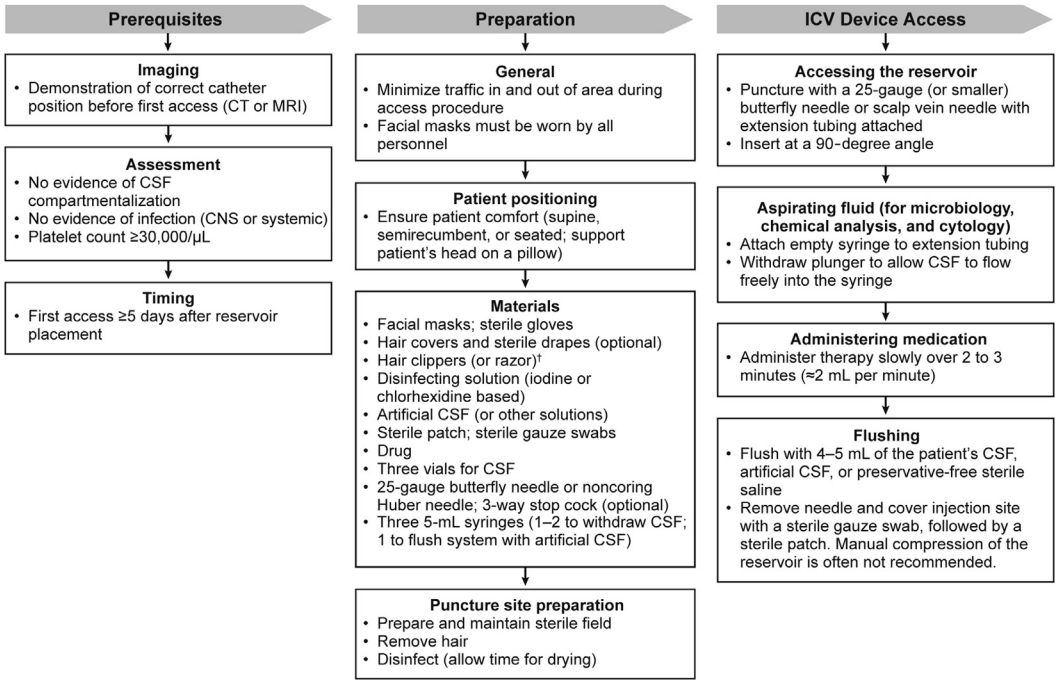

FIGURE 2.
High-level summary of individual clinics' procedures and recommended guidelines on use of ICV access devices.*[27,43] *This is not a comprehensive summary. For additional details, please refer to referenced manuscripts. †Razors may breach the skin barrier and increase the risk of infection; alternatively hair clippers or hair removal cream can be used. CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

"infection" or "experience" or "outcome"). The search was limited to articles with clinical data published in English after 1990. Articles that reported the long-term management of the ICV access point, the duration of ICV device use, and the nature and rate of complications associated with the ICV route were included in the review. Case reports and opinion pieces were excluded due to insufficient data for analysis.

Results

A total of 150 papers were identified and read in full for this review, of which 53 were excluded due to insufficient data for analysis. In the remaining 97 publications, a total of

TABLE 1.
Reported Duration of ICV Device Use and Device Presence

Reference	N	Age Range	Treatment	*In Situ* Range	*In Situ* Median
Peyrl et al. (2014)[27]	98	3 mo-21 y	Chemotherapy	31-7156 d	1336 d
Kramer et al. (2014)[28]	151	1-34 y	cRIT	1 wk-10 y	NR
Sampath et al. (2012)[49]	70	16-78 y	NR	9-33 mo	16.3 mo
Lin et al. (2012)[1]	12	4 mo-12 y	Antituberculosis treatment (isoniazid)	6-15 mo*	7.7 mo*
Shen et al. (2011)[50]	45	20-56 y	Antibiotic therapy for brain abscess	6-12 mo†	NR
Partap et al. (2011)[51]	17	31-84 y	Chemotherapy	Up to 12 mo	NR
Slavc et al. (2003)[29]	26	1.4-13.9 y	Chemotherapy	Up to 28 mo	13.5 mo
Schlegel et al. (2001)[52]	19	27-71 y	Chemotherapy	2-59 mo	31.5 mo
Esteva et al. (2000)[53]	9	32-72 y	Chemotherapy	5-58 wk	30 wk
Slavc et al. (1998)[54]	16	2-19 y	Chemotherapy	1-24 mo	NR
Czech et al. (1997)[55]	8	2-15 y	Chemotherapy	5-24 mo	NR

Abbreviations:
cRIT = Compartmental intraventricular radioimmunotherapy
d = Day
ICV = Intracerebroventricular
mo = Month
NR = Not reported
wk = Week
y = Year
* For eight children; ICV devices permanently remained in four patients.
† Twenty-five ICV devices were removed after 6-12 months *in situ*; 20 reservoirs stayed in place per patient preference. No further infections noted.

TABLE 2.
Complication Rates for Pediatric Studies (N > 50)

Reference	N*	Age Range	Indication	Duration of ICV Device Use/Presence
Peyrl et al. (2014)[27]	98	3 mo-21 y	Brain tumor (intraventricular methotrexate)	31-7156 d (median of 1336 d/device)
Pompe et al. (2012)[56]	240	<21 y	Brain tumor (intraventricular methotrexate)	NR
Brouwer et al. (2007)[45]	76	1-86 d	PHVD†	NR
Richard et al. (2001)[47]	64	3-65 d	PHVD†	NR
Bruinsma et al. (2000)[57]	70	<6 y	Hydrocephalus†	NR
Levy et al. (1997)[58]	72	3-60 d	Hydrocephalus†	NR

Abbreviations:
CSF = Cerebrospinal fluid
d = Day
ICV = Intracerebroventricular
mo = Month
NR = Not reported
OmR = Ommaya reservoir
PHVD = Posthemorrhagic ventricular dilatation
r-tPA = Recombinant-tissue plasminogen activator
y = Year
* N = number of patients <21 years of age.
† No intraventricular treatments administered unless in response to an infection.
‡ Incident with first ICV device.

5815 patients were reported to have used ICV devices. Of these 97 publications, 35 publications contained data necessary for the assessment of managing the ICV access point and for evaluation of complications and duration of use associated with the ICV route (Tables 1-5). Collectively, these 35 publications reported ICV device use in 3303 patients (Table 5). Patient ages ranged from one day to 84 years.

Duration of ICV device use

In all publications reporting long-term use of ICV access devices (*in situ* median ≥30 weeks), patients had the device implanted for one to 7156 days per device and experienced two to 280 punctures per device. Table 1 presents the duration of ICV access device use and device presence across studies.

Duration of Study/Timeframe for Data Collection	# Of ICV Device Punctures, Average (Range)	Total Number of Noninfectious Complications, n (%)	Noninfectious Complications, (n)	Total Number of Infectious Complications, n (%)	ICV Device Interventions
20 y	36 (2-280)	4 (4)	Catheter malposition (1) Kinking of the catheter at the burr-hole (1) Change in ventricular size (1) Technical failure of device (1)	1 (1)	3 removed 2 revisions 1 infection 1 surgical correction (kinking)
7 y	NR	30 (14.2)	ICV access device malfunction (14) CSF leakage (7) Combined complications (7) Other (3)	25 (11.8)	39 removed (NR)
12 y	22.3 (5-126)	14 (18.4)	Dehiscence of wound (3)	7 (9.2)	6 removed 2 infections 5 revisions (reason NR) 2 placements of a second OmR
5 y	NR	21 (33)‡	Subcutaneous CSF leak (7) Obstruction (3) CSF leak at scar (3) Local/cutaneous inflammation (2) Moving (1) General seizure (1) Dysfunction (1) Inability to tolerate tapping (1) Failure of placement (1) Death after r-tPA infusion (1)	9 (14)‡	18 removed 9 noninfectious complications 9 infections
7 y	NR	NR	NR	11 (15.9)	NR
10 y	NR	1 (1.4)	Obstruction requiring revision (1)	2 (2.8)	1 removed obstruction

Although 18 publications did not report the duration of ICV device use or the period of implantation, and 19 did not report the number of punctures per device (Tables 2-4), four studies with populations of 45 patients or more (age range, three months to 78 years) reported the continued use of ICV access devices for over six months,[27,28,49,50] and one study reported a 7156-day (approximately 19 years) maximum duration that the device was present (age range, three months to 21 years).[27] In most instances, the ICV device remained in place long after the device was used to administer therapy (Tables 1-5). In cases where the device was removed, reasons included infectious complications due to pathogenic bacteria or noninfectious complications (e.g., CSF leaks, hemorrhage, catheter malposition, catheter

TABLE 3.
Complication Rates for Adult Studies (N ≥ 50)

Reference	N*	Age Range	Indication	Duration of ICV Device Use/Presence	Duration of Study/ Timeframe for Data Collection
Zairi et al. (2011)[59]	50	28-70 y	Chemotherapy	NR	3.5 y
Chamberlain et al. (2009)[60]	84	31-84	Chemotherapy	NR	15.5 y
Boiardi et al. (2008)[61]	65	19-70 y	Chemotherapy	0-18 mo	3 y
Takahashi et al. (2007)[62]	77	17-79 y	Chemotherapy	NR	1.5 y
Ballantyne et al. (2005)[3,†]	154 ICV + 98 EP	NR	Pain management	NR	NR
Pels et al. (2003)[63]	64	27-75 y	Chemotherapy	NR	6 y
Berweiler et al. (1998)[48]	70	NR	Chemotherapy	NR	NR
Karavelis et al. (1996)[46]	90	23-80 y	Pain management	1-1362 d	9 y
Lazorthes et al. (1995)[64]	82	36-81 y	Pain management	12-443 d	10 y

Abbreviations:
d = Day
EP = Epidural
ICV = Intracerebroventricular
mo = Month
NR = Not reported
y = Year
* N = number of patients aged >17 years.
† Cochrane review.

obstruction, and device malfunction not otherwise specified).

Infectious and noninfectious complications associated with the ICV route of administration

In this analysis, complications related to the use of the ICV route rather than those resulting from the treatment administered were examined. Noninfectious complications, including intracerebral hemorrhage, catheter malposition, catheter obstruction, and subcutaneous CSF leaks, were considered separately from infectious complications. Unless otherwise noted, the reported complication rates were per patient.

Overall, for all the cohorts using ICV devices in this analysis, the noninfectious complication rates ranged from 1.0% to 33.0%, whereas infectious complication rates ranged from 0% to 27.0% (Tables 2-4). For the pediatric population (age range, one day to 21 years), long-term studies (ranging from five to 20 years) with more than 50 patients reported noninfectious complication rates ranging from 1.4% to 33.0% and infectious complication rates ranging from 1.0% to 15.9% (Table 2).[27,45,47,56-58] For adult long-term studies (ranging from 1.5 to 15.5 years) that enrolled 50 or more patients, noninfectious complication rates for ICV device use ranged from 1.2% to 9.2%, and infectious complication rates ranged from 0% to 18.5% (Table 3).[3,46,48,59,60,62-64,71] For long-term studies (ranging from two to 16 years) that included more than 50 adult and pediatric patients (combined population), the noninfectious complication rates for ICV device use ranged from 1.4% to 10.4%, and infectious complication rates ranged from 0% to 27.0% (Table 4).[5,10,28,49,65-70]

In studies that discussed the types of complications, CSF leaks, hemorrhage, catheter malposition, catheter obstruction, and device malfunction not otherwise specified were the most frequently reported noninfectious complications

# Of ICV Device Punctures, Average (Range)	Total Number of Noninfectious Complications, n (%)	Noninfectious Complications, (n)	Total Number of Infectious Complications, n (%)	ICV Device Interventions
NR	3 (6.0)	Hemorrhage (1) Bulky edema (2)	2 (4.0)	3 removed 1 infection 2 noninfectious complications
NR	NR	NR	3 (3.5)	NR
NR	6 (9.2)	Hemorrhage (6)	8 (12.3)	NR
NR	1 (1.2)	Catheter misplacement (1)	0	Revision of catheter position (1)
NR	8 (5.1) ICV + 23 (23.5) EP	ICV: malfunction (3) Leakage (3) Misplacement (1) Blockage (1) EP: leakage (5) Misplacement (3) Blockage (15)	9 (5.8) ICV + 5 (5.1) EP	NR
NR (26-30)	2 (3.1)	Catheter misplacement (1) Periventricular tumor bleeding (1)	12 (18.5)	12 removed 12 infections 3 reimplanted
NR	5 (7.1)	Moving (1) Catheter obstruction (2) Intraoperative failure of placement (2)	3 (4.3)	NR
NR	4 (4.4)	Skin erosion (1) Intracerebral hematomas (2) ICV device misplacement (1)	2 (2.2)	NR
NR	1 (1.2)	Kinking of the catheter (1)	3 (3.7)	3 removed 2 infections 1 surgical correction (kinking)

(Table 5).[10,22,66,72] The pathogens most commonly implicated in the reported infectious complications were *Staphylococcus epidermidis* and *Staphylococcus aureus* (Table 5). Infectious complications were the most frequently reported cause for device removals in the adult and combined population studies that discussed the reasons for ICV device removal. Of the 19 ICV device removals that occurred in 2.6% of the total adult population (N = 736), 14 removals (73.7%) were due to infectious complications (Table 5). Of the 82 ICV device removals that occurred in 4.2% of the combined population (N = 1947), 77 removals (93.9%) were due to infectious complications (Table 5). The reasons for ICV device removal were not included in all 69 removals that occurred in 11.1% of the pediatric population (N = 620) (Table 5). In some instances, depending on the location of the infection, infectious complications were successfully treated with ICV- and systemically administered antibiotics, thereby avoiding the removal of an ICV system.[10,13,22] A 16-year retrospective analysis of patients using ICV devices noted that 38.0% of patients with infectious complications were successfully treated with antibiotics while retaining their device.[10] However, in most cases, removal of an ICV device was necessary to treat infection. In studies that specified the rate of infectious complications per puncture, the total number of patients was 770 and the average rate was 0.45% (range, 0.2% to 0.7%).[10,22,66,72]

Discussion

The ICV route of administration has been used extensively in clinical settings for more than half a century[2] and has become an established and routine CNS delivery method for long treatment durations. Our results indicate that the ICV route of administration appears to be a safe and well-tolerated long-term method of drug delivery in both pediatric and adult patients.

TABLE 4.
Complication Rates for Studies that Combine Adult and Pediatric Patients (N ≥ 50)

Reference	N*	Age Range	Indication	Duration of ICV Device Use/Presence	Duration of study/Timeframe for Data Collection
Szvalb et al. (2014)[5]	501	6-77 y	Chemotherapy, pain management, and other	NR	10 y
Mead et al. (2014)[10]	616	NR	Cancer treatment	NR	16 y
Kramer et al. (2014)[28]	151	NR	Radioimmunotherapy	10+ y	15 y
Sampath et al. (2012)[49]	70	16-78 y	Chemotherapy	NR	2 y
Gwak et al. (2011)[65]	89§	15-76 y	Chemotherapy	NR	7.5 y
Chamberlain et al. (1997)[66]	120	10-72 y	Chemotherapy	NR	10 y
Kim et al. (1995)[67]	122	2-83 y	Ventricular drainage	NR	3 y
Cramond and Stuart (1993)[68]	52	10-82 y	Pain management	<1 wk->6 mo	6 y
Perrin et al. (1990)[69,‡]	120§	11-79 y	Chemotherapy	NR	NR
Lishner et al. (1990)[70,‡]	106	17-79 y	Cancer treatment	2 d-4.6 y (median of 4.1 mo)	6 y

Abbreviations:
CSF = Cerebrospinal fluid
d = Day
ICV = Intracerebroventricular
mo = Month
NR = Not reported
OmR = Ommaya reservoir
wk = Week
y = Year
* N = number of pediatric and adult patients.
† Complications related to therapy are not included.
‡ Populations may overlap (similar authors, complications, infections).
§ OmR patient population.

Given the long-term presence of an ICV access device, patients may have some restrictions on contact sports, but many neurosurgeons do not restrict postimplant athletic or physical activity, and the majority of patients do not request removal of the device.[28,73] Furthermore, patient complaints about the cosmetic appearance of the ICV device are infrequent.[73] In this review, only eight publications provided details about the setting (inpatient versus outpatient) where ICV therapies were administered; all specifically stated that patients were treated in an outpatient center.[2,23,28,48,50,74-76]

In this analysis, studies with relatively large populations (range, 45 to 151 patients) supported the long-term use of these devices.[27,28,49,65] ICV devices often remained in place long after treatment was finished and, in some cases, device removal was not required for treatment or correction of a

# Of ICV Device Punctures, Average (Range)	Total Number of Noninfectious Complications, n (%)	Noninfectious Complications, (n)	Total Number of Infectious Complications, n (%)	ICV Device Interventions
NR	NR	NR	40 (8)	22 removed 22 infections
NR	NR	NR	34 (5.5)	17 removed 17 infections
513 total injections for all patients (3.4)	6 (4)	Catheter migration (3) Pericatheter cyst formation (2) Shunt discontinuity (1)	0	2 removal 2 noninfectious complications 4 revisions 4 complications
NR	1 (1.4)	Malposition of catheter (1)	0	1 removed
7.3 ± 7.8	3 (3.3)	Hemorrhage (3) CSF leak (12)	13 (14.6)	12 removed 3 infections related to CSF leak 9 infections (combined for both OmR and Chemoport)
46 (10-86)	10 (8.3)[†]	Catheter obstruction (6) Catheter malpositioning (2) Exposure (2)	9 (7.5)	4 removed 2 infections 2 noninfectious complications 2 revisions
NR	NR	NR	18 Rickham (27) 7 tunneled ventriculostomy (10)	16 removed 16 infections • 14 Rickham • 2 ventriculostomy
NR	4 (7.7)	Dislodged catheter (1) Blocked catheters (3)	3 (5.8)	1 removed 1 infection
NR	11 (9.2)	Malposition of catheter (1) Malfunctioning (5) Subdural hygroma (2) Subdural hematoma (1) Mild intraventricular bleeding (2)	12 (10)	5 removed 1 noninfectious complication 4 infections 3 revisions 3 noninfectious complications
NR	11 (10.4)	Malposition of catheter (1) Subdural hygroma (2) Subdural hematoma (1) Mild intraventricular bleeding (2) Malfunctioning (5)	13 (12.3)	4 removed 4 infections

complication.[10,13,22] Nevertheless, surgical intervention to repair, revise, or remove an ICV device is important to report for any ICV cohort. It is noteworthy that no seizures were reported in the context of persisting ICV devices despite a catheter passing through the brain parenchyma. As such, the catheter tract of ICV devices appears to be equal to that of shunt catheters, which alone generally do not increase seizure frequency.[28]

Although long-term ICV access device use can result in an infectious complication in a patient,[46,64,71] long-term systemic administration of treatments by a venous access device can cause infectious complications as well.[77] The infection rate for peripherally inserted central catheters has been documented as 0.75 infections per 1000 catheter-days,[78,79] and a 2014 study (N = 616) reported a very similar infection rate for Ommaya reservoirs of 0.74 infections per

TABLE 5.
Summary of Complications and ICV Device Removals for all Studies

Population	N	Total Number of Noninfectious Complications (% of Population)	Noninfectious Complications (n)*	Total Number of Infectious Complications (% of Population)	Pathogen (n)*	ICV Device Interventions* (% of Population)
Pediatrics (Table 2)	620	70 (11.3%)	Subcutaneous/scar CSF leak (17) Malfunction (16) Combined (7) Obstruction/ kinking (5) Malposition/ moving/failure of placement (3) Wound dehiscence (3) Other (3) Local/cutaneous inflammation (2) General seizure (1) Inability to tolerate tapping (1) Change in ventricular size (1) Death after r-tPA infusion (1)	55 (8.9%)	*Staphylococcus epidermidis* (12) *Staphylococcus aureus* (2) *Candida albicans* (2) Nonspecific (2) *Bacillus cereus* (1) *Enterobacter cloacae* (1) CoNS (NR)	69 removed (11.1%) 12 noninfectious complications 12 infections 45 not reported
Adult (Table 3)	736	30 (4.1%)	Hematoma/ hemorrhage/ bleeding (10) Malposition/ moving/ misplacement (7) Obstruction/ kinking (4) Subcutaneous/scar CSF leak (3) Malfunction (3) Edema (2) Wound dehiscence (1)	42 (5.7%)	Nonspecific (37) *Staphylococcus aureus* (3) *Staphylococcus epidermidis* (1) *Enterobacter cloacae* (1)	19 removed (2.6%) 4 noninfectious complications 14 infections 1 not reported
Combined (Table 4)	1947	46 (2.4%)	Hematoma/ hygroma/ bleeding (13) Malposition/ moving/ misplacement (9) Obstruction/ kinking (10) CSF leak (12) Malfunction (10) Cyst formation (2) Wound dehiscence (2)	142 (7.3%)	CoNS (61) Nonspecific (22) *Staphylococcus epidermidis* (20) *Propionibacterium acnes* (16) *Staphylococcus aureus* (6) *Streptococcus* species (5) Other *Staphylococcus* species (4) *Pseudomonas* spp. (4) Diphtheroids (4) MSSA (4) *Candida parapsilosis* (3) Other (7)	82 removed (4.2%) 5 noninfectious complications 77 infections

Abbreviations:
CoNS = Coagulase-negative *Staphylococcus*
CSF = Cerebrospinal fluid
ICV = Intracerebroventricular
MSSA = Methicillin-sensitive *Staphylococcus aureus*
NR = Not reported
r-tPA = Recombinant-tissue plasminogen activator
* Not all complications, infections, and/or interventions were detailed in the publications and therefore numbers will not sum to the total.

10,000 Ommaya-days.[10] The infectious complications most frequently implicated during ICV device use are due to skin flora,[10,70,80,81] and the use of strict aseptic techniques has been shown to reduce the frequency of these types of complications.[27] Many studies indicate that a clinician's experience and training with the use of aseptic techniques when accessing ICV devices can reduce infection rates and facilitate the long-term use of ICV devices,[27,44-47] and a number of studies note that applying best practices can reduce or prevent complications.[27,28,49,50] As ICV devices are now used for long-term administration of treatment, best practice guidelines for the management of ICV devices and prevention of infection are urgently needed.[10]

Very few of the publications in this analysis reported infectious complication rates per puncture or per administration, and a difference in the metrics used made it challenging to determine the specific infection rate per puncture. However, this is a critical metric given the relationship between punctures and infections. We recommend that noninfectious complications are reported per device-year, and infectious complications are reported per puncture in future studies that include the use of ICV devices.

In this review, complication rates were compared across studies. However, differences in these rates may have been due to differences in aseptic technique, surgical methods, patient characteristics, or even the type of therapy delivered. Additionally, surgical and aseptic procedures have improved since many of these articles were published more than ten years ago.[2,20,82] Nevertheless, this review of the literature demonstrates that the ICV route is an established and well-tolerated method for chronic CNS drug delivery in pediatric and adult populations. Although there are infectious and noninfectious complication risks associated with the use of ICV access devices, the complications are manageable and can be minimized with proper care and experience. Applying best practices can substantially mitigate infectious complications associated with ICV access devices and promote long-term use.

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