Implantable Infusion Pump

Description

Implantable infusion pumps can provide long-term drug infusion at constant or variable rates. Primary uses are delivery of chemotherapy agents and analgesics; several devices are commercially available.

Background

An implantable infusion pump is intended to provide long-term continuous or intermittent drug infusion. Possible routes of administration include intravenous, intra-arterial, subcutaneous, intraperitoneal, intrathecal, and epidural. The implantable infusion pump is surgically placed in a subcutaneous pocket under the infraclavicular fossa or in the abdominal wall, and a catheter is threaded into the desired position. Intrathecal and epidural catheter positions are both intraspinal; however, the intrathecal position is located in the subarachnoid space, which is past the epidural space and dura mater and through the theca of the spinal cord.

A drug is infused over an extended period of time and may be delivered at a constant or variable rate by calibrating the implantable infusion pump per physician specifications. The drug reservoir may be refilled as needed by an external needle injection through a self-sealing septum in the implantable infusion pump. Bacteriostatic water or physiological saline is often used to dilute drugs. A heparinized saline solution may also be used during an interruption of drug therapy to maintain catheter patency.

The driving mechanisms may include peristalsis, fluorocarbon propellant, osmotic pressure, piezoelectric disk benders, or the combination of osmotic pressure with an oscillating piston.

Regulatory Status

Several implantable infusion pumps have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process, including but not limited to the Medtronic SynchroMed® (Fridley, MN) family of pumps, the Medtronic IsoMed® infusion system (Minneapolis, MN; the Flowonix™ Prometra® programmable pump (Mount Olive, NJ); and Shiley Infusaid® pumps (Norwood, MA). In August 2012, the FDA approved the MedStream™ Programmable Infusion System (Codman and Shurtleff- a division of DePuy), which includes an implantable pump, for intrathecal delivery of baclofen in patients with spasticity.
Implantable infusion pumps are considered **medically necessary** when used to deliver drugs having FDA approval for this route of access and for the related indication for the treatment of:

- Cancer in the following situations:
  - Primary liver cancer (intrahepatic artery injection of chemotherapeutic agents);
  - Metastatic colorectal cancer where metastases are limited to the liver (intrahepatic artery injection of chemotherapeutic agents);
  - Primary epithelial ovarian cancer (intraperitoneal infusion as component of chemotherapy);
- Severe, chronic, intractable pain (intravenous, intrathecal, and epidural injection of opioids), following a successful temporary trial of opioid or non-opioid analgesics by the same route of administration as the planned treatment. A successful trial is defined as greater than 50% reduction in pain following implementation of treatment; and
- Severe spasticity of cerebral or spinal cord origin in patients who are unresponsive to or who cannot tolerate oral baclofen therapy (intrathecal injection of baclofen).

Implantable infusion pumps are considered **investigational** for all other uses (e.g., chemotherapy for patients with head and neck cancers, gastric cancer, bone or soft tissue sarcoma, or skin cancer; heparin for thromboembolic disease, insulin for diabetes, antibiotics for osteomyelitis).

**Rationale**

**Chemotherapy for Cancer Patients**

**Primary liver cancer**

No randomized controlled trials (RCTs) have evaluated whether hepatic arterial infusion of chemotherapy in patients with primary liver cancer improves health outcomes. A 2013 comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ) evaluated local therapies for unresectable primary hepatocellular carcinoma in patients ineligible for surgical resection or transplantation (1) Treatments reviewed included ablative therapies (e.g., radiofrequency ablation), radiotherapy (e.g., intraluminal brachytherapy) and embolization (e.g., transarterial embolization either
with [TACE] or without [TAE] chemotherapy). Although TACE delivers chemotherapy and embolic materials through hepatic arterial infusion, this procedure generally is performed by an interventional radiologist and does not require implantation of an infusion pump. Thus, this AHRQ report does not address the use of implantable infusion pumps for delivery of chemotherapy for primary liver cancer.

Several case series were identified. Most recently, Jarnagin and colleagues (2009) reported on 34 patients with unresectable primary liver cancer who received hepatic arterial infusion of floxuridine and dexamethasone. (2) Sixteen of 34 (47%) patients had a partial response to treatment. Median survival was 29.5 months; the 2-year survival rate was 67%. In addition, Smith and colleagues (1984) studied 11 patients and found a complete response to chemotherapy in 1 patient and partial responses in 6 patients. (3) Atiq and colleagues found a partial response in 4 of 10 (40%) of patients with unresectable liver cancer treated with intrahepatic chemotherapy delivered through an implantable pump. (4) The evidence is limited but suggests that some patients, with limited other treatment options, may benefit from arterial infusion of chemotherapy.

Liver metastases from colorectal cancer

A 2012 AHRQ comparative effectiveness review evaluated local hepatic therapies for colorectal cancer metastases in patients ineligible for systemic chemotherapy. (5) Like the AHRQ review mentioned above, local therapies included ablation, radiotherapy, and embolization. Four case series of chemotherapy delivered via hepatic artery infusion by an indwelling pump were identified. Two retrospective case series assessed a total of 67 patients who were refractory to systemic chemotherapy, and 2 case series assessed a total of 36 patients who received concomitant systemic chemotherapy. Infused chemotherapies were mitomycin plus gemcitabine or 5-fluorouracil; systemic chemotherapy regimens varied. Median overall survival was 9.7 months and 6.7 months in the refractory group, and 30.1 months and 22.0 months in the systemic chemotherapy group. Grade 3 adverse events attributed to hepatic artery infusion included leukocytopenia, hyperbilirubinemia, hypersensitivity reaction, and neuropathy. This evidence was considered insufficient to form any conclusion about the comparative benefits (e.g., overall survival, quality of life) or harms (i.e., adverse events) of hepatic artery infusion for these patients.

For patients who are eligible for systemic chemotherapy, a 2009, Cochrane review compared hepatic arterial infusion versus systemic chemotherapy for patients with unresectable liver metastases from colorectal cancer. (6) Ten RCTs that evaluated a total of 1,277 patients were included. Nine of these provided data on tumor response. The response rate was significantly higher in the hepatic arterial infusion group (198 of 461, 43%) than the systemic chemotherapy group (81 of 440, 18%). The pooled risk ratio (RR) was 2.26 (95% confidence interval [CI]: 1.80-2.84). However, there was not a significantly higher survival rate associated with hepatic arterial infusion chemotherapy. The mean weighted median overall survival times were 15.9 months with hepatic arterial infusion chemotherapy and 12.4 months for systemic chemotherapy (pooled hazard ratio: 0.90; 95% CI: 0.76-1.07). Adverse effects and quality-of-life outcomes were not reported.

Ammori et al (2014) reported on a cohort of 373 patients with unresectable colorectal liver metastases who received hepatic artery infusional chemotherapy and systemic chemotherapy at a single U.S. center.(7) The primary outcome was the proportion of patients who converted to complete resection or
ablation. Two patients died due to postoperative complications after pump placement; adverse events (AEs) associated with the pump (e.g., biliary sclerosis, malfunction) occurred in 13% of patients. Ninety-three patients (25%) achieved the primary outcome at a median of 7 months. Median and estimated 5-year survival (from the time of pump placement) was 59 months and 47%, respectively, in patients who underwent resection or ablation, and 16 months and 6%, respectively, in patients who did not (log-rank test, p<0.001).

This evidence suggests that arterial infusion of chemotherapy improves response rates for patients with colorectal cancer metastatic to the liver compared to systemic chemotherapy. The impact on survival is uncertain.

**Head and neck cancers**

Several studies have evaluated interventions that combine radiotherapy and concomitant intra-arterial cisplatin (known as RADPLAT) on patients with head and neck cancer. These studies used intra-arterial delivery of cisplatin via an intra-arterial catheter rather than an implantable pump. Although an implantable infusion pump was not used, the principle of treatment is similar, so that these studies have some relevance to the evaluation of infusion pumps.

In 2006, Hoebers and colleagues in The Netherlands randomized patients with stage III or IV head and neck squamous cell carcinoma to radiotherapy with standard intravenous (IV) cisplatin (n=21) or high-dose intra-arterial cisplatin (n=14). (8) Rates of acute mucositis and hematological toxicity did not differ significantly between groups; however, there was a higher rate of acute renal toxicity in the IV group (30%) compared to the intra-arterial group (0%). Over 2 years, there were no significant differences between treatment groups in locoregional control of disease, disease-free survival, or overall survival.

A study by Ackerstaff and colleagues examined 17 quality-of-life scales at several time points after treatment with radiotherapy with intravenous or intra-arterial cisplatin. (9) The study included 207 patients with inoperable advanced head and neck cancer. The only statistically significant difference between groups was in the nausea/vomiting scale at 7 weeks, at which time the rate of symptoms were higher in the intravenous compared to the intra-arterial group. Otherwise, quality-of-life symptoms were similar in the 2 groups.

Evidence from 2 RCTs did not find a clear advantage of intra-arterial chemotherapy delivered via an intra-arterial catheter compared to IV chemotherapy in combination with radiotherapy for patients with head and neck cancer. Therefore, it is not likely that similar agents delivered via an implantable infusion pump would improve outcomes.

**Primary epithelial ovarian cancer**

A 2011 Cochrane review examined literature on whether an intraperitoneal (IP) component of chemotherapy improves ovarian cancer outcomes compared to intravenous chemotherapy-only. (10) Nine RCTs with a total of 2,119 patients were identified; 6 trials were considered high-quality. In a pooled analysis of data from 8 trials, there was a significantly lower rate of mortality with an IP component of chemotherapy compared to no IP component (hazard ratio [HR]: 0.81; 95% CI: 0.72 to 0.90). Moreover, a pooled analysis of data from 5 trials found that an IP component of chemotherapy is associated with a significantly longer disease-free interval (HR: 0.78; 95% CI: 0.70 to 0.86). However,
an IP component of chemotherapy was associated with significantly more adverse effects (e.g., infection, fever, pain, and gastrointestinal symptoms). For example, a pooled analysis of 3 studies found a significantly higher infection rate when there was an IP component of chemotherapy compared to IV-only chemotherapy (RR: 3.34, 95% CI: 2.06 to 5.43).

An example of one of the individual RCTs is a high-quality RCT with a relatively large number of patients published by Markman and colleagues in 2001. (11) This was a multicenter study conducted in the United States and included women diagnosed with stage III epithelial ovarian cancer that entered the study within 6 weeks of surgery. Patients were randomized to receive either standard dose IV cisplatin/paclitaxel for 6 courses or 2 cycles of moderately high-dose carboplatin, followed by 6 courses of IV paclitaxel and intraperitoneal cisplatin. A total of 523 patients entered the trial, and 61 (12%) were subsequently found to be ineligible for reasons including the wrong stage of cancer or inadequate surgery. Of the remaining 462 eligible patients, 227 were in the IV chemotherapy-only group and 235 were in the intraperitoneal component chemotherapy group. At the time of data analysis, 103 of 227 (45.4%) patients in the IV-only group and 126 of 235 (53.6%) in the IP-component chemotherapy group were still alive. Improvement in survival with IP chemotherapy that was of borderline statistical significance (RR: 0.81; 95% CI: 0.65 to 1.00). Progression-free survival was significantly longer in the IP chemotherapy-component group compared to the IV chemotherapy-only group (median time to recurrence: 27.9 months vs. 22.2 months, respectively, p=0.01). Several adverse events occurred more commonly in the IP chemotherapy component group compared to the IV-chemotherapy-only group. These included grade 3-4 gastrointestinal events (37% vs. 17%, respectively) and platelet toxicity (49% vs. 3%, respectively). Two patients in each group died of causes considered to be related to chemotherapy.

Evidence from multiple RCTs, including some of high-quality, and systematic reviews, indicates that intraperitoneal chemotherapy for patients with primary epithelial ovarian cancer has a significant impact on progression-free survival and likely also improves overall survival. This benefit is accompanied by an increased risk of adverse effects with intraperitoneal infusions, including infections, pain, and gastrointestinal symptoms.

**Gastric cancer**

A 2011 systematic review examined RCTs and observational studies on intraperitoneal chemotherapy used to treat gastric cancer. (12) The authors identified 14 studies, 2 RCTs, 2 case-control studies and 10 observational studies. One of the RCTs compared groups of patients who did and did not receive intraperitoneal taurolidine following tumor resection and did not find statistically significant differences in outcomes. The other RCT (n=118) found a significantly higher rate of survival in patients who received either IP chemotherapy plus intraoperative peritoneal lavage or IP chemotherapy-only in addition to surgery versus surgery only. (Additionally, all patients in the second study received adjuvant oral 5-fluorouracil derivatives for 2 years.) The authors of the systematic review recommended that future studies evaluate preoperative or intraoperative IP chemotherapy in association with systemic chemotherapy. This evidence on intraperitoneal chemotherapy for treating gastric cancer is insufficient to determine whether health outcomes are improved.
Mixed Sarcoma and Skin Cancers
Liu et al (2014) reported on a cohort of 31 patients with ulcerative skin cancers or sarcomas who received intra-arterial chemotherapy at a single center in China. Patients had squamous cell skin carcinoma (n=9), synovial sarcoma (n=6), malignant fibrous histiocytoma (n=5), liposarcoma (n=3), osteosarcoma (n=3), malignant melanoma (n=2), epidermoid sarcoma (n=2), or dermatofibrosarcoma protuberans (n=1). Infusion pumps were implanted in subcutaneous tissue near the involved subclavian artery for 10 patients with upper extremity disease and near the involved femoral artery for 21 patients with lower extremity disease. All patients received intra-arterial cisplatin and epirubicin at 2- to 3-week intervals for 2 (n=9) or 3 (n=22) cycles; patients with squamous cell carcinoma additionally received bleomycin, and patients with melanoma received dacarbazine. Twenty-seven patients (87%) achieved pain remission; 19 patients (61%) had complete remission (no pain), and 8 patients (26%) had partial remission (significantly reduced pain with uninterrupted sleep and normal life). Nineteen patients underwent tumor resection after tumor shrinkage with chemotherapy. Using World Health Organization criteria for chemotherapy response in ulcerating tumors, 22 patients (71%) achieved remission; 7 patients (23%) had complete remission (complete healing without rerupture for >1 month), and 15 patients (48%) had partial remission (50% shrinkage of the ulcer surface without rerupture for >1 month). Three patients had tumor recurrence, and 3 patients underwent lower leg amputation. Among 19 patients who underwent local tumor resection after chemotherapy-induced tumor shrinkage, local chemotherapy reaction by pathologic examination of excised tissue was observed in all patients, half of which were severe. Other AEs included gastrointestinal effects, bone marrow suppression, and visceral injury, which were considered milder than seen with traditional chemotherapy. Due to lack of a control group, relative improvement in net health outcomes in comparison with current treatments is unknown. Therefore, implanted infusion pumps to deliver chemotherapy in patients with sarcoma and ulcerative skin cancers are considered investigational.

Pain
Cancer pain

One systematic review of the literature was identified; it was published in 2010 by Myers and colleagues. They identified 12 RCTs on intraspinal techniques for managing pain in cancer patients; studies are required to report pain as an outcome measure using a validated scale. The investigators did not identify the type or types of cancer addressed in individual studies and did not pool study findings. Two RCTs specifically addressed implantable infusion pumps. One compared intrathecal morphine delivered via an implantable infusion pump plus medical management (n=101) to medical management alone (n=99) in patients with refractory cancer pain. The difference between groups in clinical success (defined as at least 20% reduction in pain score and at least 20% reduction in drug toxicity at 4 weeks) reached borderline statistical significance, favoring the implantable pump group over the control group (85% vs. 71%, respectively, p=0.05). The proportion of patients who experienced pain a minimum 20% pain score reduction was 52% in the implantable pump group and 39% in the control group; this was not a statistically significant difference (p=0.55). The other RCT on implantable pumps compared epidural morphine delivered as a continuous infusion by the Infusaid pump to intermittent delivery by a Port-a-Cath® (Deltec, Saint Paul, MN). The 2 groups did not differ significantly in their pain scores; scores were low in both groups and the study, which had only 29 participants, was likely underpowered. The evidence from this systematic review indicates that
Intraspinal techniques may be appropriate for selected cancer patients with intractable cancer pain but there is a shortage of high-quality RCTs.

Noncancer pain

In 2013, the American Society of Interventional Pain Physicians (Falco et al.) published a systematic review of intrathecal infusion for the treatment of chronic non-cancer pain. (15) The outcome of interest was pain relief, defined as a minimum 50% reduction of pain in at least 40% of patients, or a minimum 3-point reduction in pain scores. Both short-term (less than 12 months) and long-term (12 months or longer) outcomes were considered. Twenty-eight studies were identified, but 21 were excluded for not meeting one or more inclusion criteria (e.g., outcomes not related to pain relief; sample size less than 50; minimum quality assessment). All 7 included studies were retrospective or prospective cohort studies. Six studies that each reported short-term (668 patients) or long-term (637 patients) pain outcomes indicated reduced pain with intrathecal opioids. The authors concluded that evidence for intrathecal opioid infusion in chronic non-cancer pain is limited. Suggested contraindications to intrathecal opioid therapy (e.g., active infection) and indications to proceed with therapy (e.g., oral opioid therapy contraindicated) are provided.

In 2009 Patel and colleagues published a systematic review of intrathecal infusion pumps used to treat chronic non-cancer pain. (16) Included studies evaluated an intrathecal device (programmable or fixed infusion rate), stated a specific indication and the drug that was injected, followed patients for at least 12 months, and included at least 25 patients. In addition, the investigators rated study quality; included studies scored at least 50 out of 100 on a methodologic quality scale. The primary outcome of interest to the systematic review was pain relief. A total of 15 studies on intrathecal infusion for non-cancer pain were identified; however, 6 did not have sufficient follow-up, 4 included fewer than 25 patients, and 1 had unacceptably low quality, leaving 4 eligible studies. All of the studies were observational and involved intrathecal opioid administration; sample sizes ranged from 69 to 120. Most patients experienced lumbospinal pain. Two of the 4 studies showed positive results for pain relief, one study had negative results, and results were unavailable for the fourth study. The authors of the systematic review acknowledged the paucity of literature and lack of RCTs. Using the grading system developed by Guyatt and colleagues, the authors concluded that a 1C recommendation for the use of intrathecal infusion systems in chronic noncancer pain was appropriate; that is, a strong recommendation based on low-quality or very low-quality evidence in which the benefits outweigh the risks and the recommendation may change when higher quality evidence becomes available. (17)

In 2012, Hamza and colleagues published a 36-month prospective cohort study of low-dose intrathecal (IT) opioids for chronic nonmalignant pain using the Synchromed II programmable pump. (18) Sixty-one patients with severe intractable pain who had failed multiple lines of pain therapy and were referred for IT treatment underwent a blinded trial of IT opioids. Three patients who experienced pain relief in response to saline were excluded. Mean age of the 58 included patients was 59±14 years, and mean duration of symptoms was 6±2 years. Pain syndromes were failed back surgery syndrome in 60% of patients, chronic low back pain in 28%, and chronic complex regional pain syndrome, abdominal pain, or pelvic pain in 12%. All patients were weaned from opioids for 7-10 days before pump implantation and participated in a 12-week physical therapy program commencing at 8 weeks post-implant. At 36 months, there was a 55% reduction from baseline worst pain score (from 8.91 to 4.02 on the Brief Pain Inventory [BPI] 0-10 scale; p=0.012) and a 54% reduction from baseline average pain score (from 7.47
to 3.41; p<0.001). Improvements in physical function and behavior (mood, relations, and sleep) as measured by the BPI also were statistically significant. Mean IT opioid dose increased 11% from 1.4 to 1.6 morphine equivalents daily. Mean oral opioid dose decreased 97% from 129 to 4 morphine equivalents daily. Adverse events were reported to be mild and limited (wound infection and pruritus in 3 patients [5%] each; peripheral edema and seroma in 2 patients [3%] each).

Several additional case series were identified in recent literature searches. In 2010, Alti and colleagues published a single-center study conducted in the United States. (19) This was a retrospective review of outcomes in 57 patients referred for pain management at a single center who received an implanted intrathecal infusion pump. Twenty-eight of the 57 (49%) patients had failed back surgery syndrome, 16 (28%) had neuropathic pain, and the remaining 13 (23%) had a variety of different diagnoses. Preservative-free opioid (usually morphine) was infused, and patients could also receive oral opioid; adjustments in dosage could be made at any time. Forty-nine of 57 patients (86%) completed the 3-year follow-up. At the time of the first pump refill (3-6 months), 23 of 49 (47%) study completers reported having at least a 50% reduction in pain from baseline, as measured on a 10-point visual analogue scale. The proportion of responders decreased over time; at the 3-year follow-up, 9 of 49 (18%) had at least a 50% reduction in pain from baseline. The 9 patients represented 39% of those who met the at least 50% criterion at the first refill. The use of oral opioids was significantly lower at the 1- and 3-year follow-ups than at baseline (p values not reported). The mean baseline oral opioid dose in morphine or its equivalent was 184 mg/24 hours. At 1 and 3 years, mean doses were 44 mg/24 hours and 58 mg/24 hours, respectively. At 3 years, 12 of 49 (25%) patients had ceased all oral opioid use. In contrast, the mean dose of intrathecal opioids significantly increased during follow-up, compared to the dose at discharge after pump implantation. The mean dose at discharge was 6.5 mg/24 hours, at 1 year was 9.3 mg/24 hours, and at 3 years was 12.2 mg/24 hours. Complications occurred in 10 of 57 (17.5%) patients; these included 5 infections, 3 catheter revisions, 2 seromas at the pump site, and 2 intrathecal granulomas. Another retrospective case series conducted in the United States and published in 2011 included 126 non-cancer intractable pain patients. (20) Patients received intrathecal opioids-only (n=72) or opioids and bupivacaine (n=54). Outcomes were evaluated 12 months after pump implantation. Pain intensity was assessed using an 11-point numeric rating scale (NRS) where 0=no pain and 10=the worst imaginable pain. In the group that began with opioids only, mean pain intensity score decreased significantly from 7.42 (standard deviation [SD]: 2.1) at baseline to 5.85 (SD: 2.8) at 12 months, p<0.001. In the opioid plus bupivacaine group, the mean pain intensity score decreased from 7.35 (SD: 2.1) at baseline to 5.03 (SD: 2.4) at 12 months, p<0.001.

In 2012, Duarte and colleagues in the U.K. published a case series with long-term follow-up on 20 patients with chronic nonmalignant pain who received intrathecal delivery of opioid analgesics. (21) Patients were followed for a mean of 13.5 years (range: 10.4 to 17.9 years). At 4-year and 13-year assessments, outcomes were significantly improved compared to baseline. However, outcomes did not significantly improve between 4 and 13 years. For example, mean pain intensity (measured on an 11-point scale where 0 represents no pain and 10 represents the worst pain) was 8.65 (SD: 0.29) at baseline, 4.95 (SD: 0.53) at 4 years post-treatment, and 5.30 (SD: 0.35) at 13 years post-treatment. Similarly, mean quality-of-life score (0 represents no interference with quality of life and 10 represents maximum interference) was 8.45 (SD: 0.49) at baseline, 4.95 (SD: 0.69) at 4 years, and 4.45 (SD: 0.48) at 13 years.
In summary, evidence on the use of infusion pumps for chronic, non-cancer pain consists of numerous uncontrolled observational studies. These studies, which are limited methodologically, report that pain and quality of life is improved with the use of infusion pumps.

Severe spasticity

The evidence base comprises observational studies and 2 systematic reviews of these studies. A 2014 systematic review of intrathecal baclofen for spasticity in patients with traumatic or nontraumatic spinal cord injury identified 8 studies (total N=162).(22) At follow-up (range, 2-41 months), reductions in mean Modified Ashworth Scale (scored 0-5) were statistically significant, from 3.1 to 4.5 (limb rigidity or considerable increase in tone) at baseline to 1.0 to 2.0 (slight increase in tone); p<0.005). AEs associated with baclofen, pump/catheter malfunction (e.g., dislodging, kinking, breaking), and infections/seromas at the incision site were reported. Baclofen overdose in 3 patients (2%) and withdrawal seizure in 1 patient (<1%) were attributed to pump malfunction.

The other systematic review, published in 2011 by Pin and colleagues, focused on intrathecal baclofen therapy for spasticity and/or dystonia of cerebral origin. (23) The authors identified 16 uncontrolled studies with a total of 227 participants. All studies were judged to be of low quality. Most outcomes were intermediate measures (i.e., at the level of body structures or functions) such as range of motion and muscle strength; several studies used objective outcomes (e.g., motor function at the level of activities or participation as assessed by the Gross Morot Function Measure, laboratory-based gait analysis, or gait assessment tools). The authors’ interpretation of the studies was that they showed a higher rate of benefit with intrathecal baclofen therapy in patients who were already ambulatory. Adverse events were not consistently defined and reported but appeared to be common. One study that used objective outcomes was published in 2011 by Motta and colleagues in Italy. (24) This study found a statistically significant increase in the Gross Motor Function Measure (GMFM) score after 1 year. Median GMFM score (as a percentage of maximum score) in 30 cerebral palsy patients with spasticity who received intrathecal baclofen increased from 65.0 to 69.4, p=0004.

In 2011 (after the Pin et al. literature search), Morton and colleagues in the U.K. published findings of a non-randomized controlled study of intrathecal baclofen therapy in non-ambulant children with severe spastic cerebral palsy. (25) Patients who responded to a one-time test dose of 50 ug intrathecal baclofen were fitted for a pump and placed on a waiting list for surgery. The investigators compared patients who had been on the waiting list between 6-12 months (group 1, n=18) to patients who had undergone surgery (group 2, n=20). Mean time between baseline and outcome assessment was 8.5 months in group 1 and 9.5 months in group 2. There was not a statistically significant difference between the 2 groups in the primary outcome measure, the Pediatric Evaluation of Disability Inventory (PEDI). The authors noted, however, that given the small number of patients recruited, the study was underpowered to detect clinically significant differences between groups on this outcome. Several secondary outcomes favored group 2, including scores on the Modified Ashworth Scale (difference between groups 1.7, p=0.008), scores on the Penn Spasm Scale (difference between groups -1.3, p=0.0010) and the range-of-motion score (difference between groups 8.3, p=0.005).

A small 2012 study compared mode of administration of intrathecal baclofen in 38 adults with muscle hypertonia due to brain injury or spinal cord disorder who were receiving intrathecal baclofen. (26) Pumps were programmed to deliver a single daily bolus of baclofen with low background continuous
dose (intervention group) or a continuous equivalent daily dose (controls). For patients receiving 75-85 mg of baclofen daily, a neurophysiologic measure of spasticity (H-reflex in the soleus [calf] muscle) improved statistically significantly more in the intervention group than in controls. For patients receiving 100-150 mg of baclofen daily, the difference between groups was not statistically significant.

Several authors have reported on long-term (1-14 years) outcomes in patients receiving intrathecal baclofen for treatment of intractable spasticity or dystonia.

- Of 158 adults at a single center in France, 28 (18%) experienced an AE within 12 months of surgical insertion of the pump. (27) Most AEs (58%) occurred during the first month after surgery and were commonly related to the insertion site (scar dehiscence, hematoma; 53%), device dysfunction or migration (29%), and adverse effects of baclofen (18%).

- Margetis et al (2014) reported 2-year outcomes of 14 ambulatory adults with hereditary spastic paraplegia. (28) All patients experienced a reduction in lower limb spasticity as measured by Modified Ashworth Scale; mean (SD) scores reduced from 2.6 (0.8) (slight-to-moderate increase in tone) to 0.7 (0.9) (no-to-slight increase in tone; paired samples t-test, p=0.000). Walking ability as assessed by a modified pediatric scale (functional walking scale of the Gillette Functional Assessment Questionnaire, scored 1-10) improved from a mean (SD) of 5.9 (1.7) (walks more than 15-50 feet outside but uses a wheelchair for community distances) to 7.4 (2.0) (walks community distances but requires moderate assistance on uneven terrain, e.g., curbs; paired samples t-test, p=0.001). A responder analysis was not reported. Adverse events included catheter fracture in 2 patients.

- Ghosh et al (2013) reported 3-year experience of 119 children (mean age, 13 years) at a single U.S. center. (29) Five patients (4%) underwent pump removal due to lack of efficacy. Mechanical complications requiring pump and/or catheter revision occurred in 19%, infections in 22%, and meningitis in 6%.

- Vles et al (2013) reported long-term (6-9 years) follow-up of 17 non-ambulant children (mean age at enrollment: 13 years) with cerebral palsy who had participated in a Dutch trial of continuous intrathecal baclofen. (30) Previously observed positive effects on pain, ease of care, and mental health of the child were maintained at follow-up.

- Of 430 children (mean age, 13 years) followed for a mean of 8 years at a single center in Italy, 25% had 1 or more complications: 15% experienced a problem with the catheter (most commonly within 12 months after implant), 9% experienced an infection, 5% a cerebrospinal fluid leak, and 1% a problem related to the pump. (31)

- At 10 years or more of follow-up, 24 adults at a single U.S. outpatient spasticity clinic reported on average: low levels of pain, moderate life satisfaction, infrequent spasms (mild-to-moderate severity), and few adverse effects (normal sleepiness, low-to-moderate fatigue). (32)

In summary, evidence from case series and nonrandomized, comparative studies report improvements in spasticity for patients treated via implantable infusion pumps. However, high-quality RCTs to confirm this benefit are lacking.
Implanted Infusion Pumps for Other Indications

Type 1 Diabetes Mellitus
A small body of literature reports on outcomes of continuous peritoneal insulin infusion (CPII) for patients with poorly controlled type I diabetes mellitus (DM), including a few small RCTs and a systematic review that included several RCTs. (33-35) These studies reported decreased hypoglycemic episodes, and some reported improved glucose control compared with usual care. However, larger, high-quality trials are needed to determine whether this approach improves outcomes and whether it is equivalent to treatment alternatives for patients with poorly controlled type I DM.

Systematic reviews, meta-analyses, or large RCTs on the use of implanted infusion pumps for other indications were not identified.

Ongoing and Unpublished Clinical Trials
A search of online site ClinicalTrials.gov identified 2 ongoing RCTs that are evaluating the use of implantable infusion pumps in a variety of conditions. These are listed next.

SISTERS: Spasticity in Stroke Study (NCT01032239): This RCT compares intrathecal baclofen therapy to best medical treatment for patients with severe spasticity at least 6 months following stroke. The primary outcome is change in the Ashworth scale. Estimated enrollment is 88 patients, and the expected date of completion is March 2017.

Regional Versus Systemic Chemotherapy in the Treatment of Unresectable Pancreatic Cancer (NCT01665625): This open-label RCT compares systemic gemcitabine therapy to continuous regional delivery of gemcitabine using an implanted percutaneous left subclavian artery port-catheter drug delivery system in patients with inoperable pancreatic carcinoma. The primary outcome is overall survival. Estimated enrollment is 90 patients, and the expected date of completion is February 2016.

Additionally, Bonouvrière et al are conducting an RCT in 30 children (age, 4-25 years) with dystonic cerebral palsy.(36) Patients will be randomized to 3 months of continuous intrathecal baclofen or placebo, after which all patients will receive intrathecal baclofen for 9 months due to ethical concerns related to placebo treatment for longer than 3 months in this population. The primary efficacy outcome is change in activities of and participation in daily life measured by Goal Attainment Scaling at 3 and 12 months. Individualized goals and definitions of response in Goal Attainment Scaling permits are scored in a standardized way to permit comparisons between groups. Secondary outcomes include changes in dystonia, spasticity, pain, comfort, and sleep-related breathing disorders. (Netherlands Trial Register: NTR3642)
Practice Guidelines and Position Statements

Cancer Treatment
Current guidelines (2014) from the National Comprehensive Cancer Network (NCCN) include the following statements:

- Colon cancer
  - “Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (e.g., hepatic arterial infusion [HAI]) remains an option.” (37)

- Hepatocellular carcinoma
  - Intra-arterial chemotherapy is recommended as a treatment option for patients with unresectable disease who are not transplant candidates (Category 2A recommendation: based on lower level evidence with uniform NCCN consensus that the intervention is appropriate). (38)

- Intrahepatic cholangiocarcinoma
  - For patients with unresectable or metastatic disease, and for patients with residual local disease post-resection, systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers (Category 2A recommendation).(38)

- Ovarian cancer
  - Intraperitoneal chemotherapy is recommended for patients with stage 2-3 disease, with less than 1 cm optimally debulked tumor (Category 1 recommendation for stage 3 disease: based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2A recommendation for stage 2 disease). (39)

Current NCCN guidelines for head and neck cancers,(40) soft tissue sarcoma,(41) bone cancer, (42) basal and squamous cell skin cancers,(43) and melanoma (44) do not include implantable infusion pumps. Isolated limb perfusion/infusion, which is a treatment option for select patients with unresectable soft tissue sarcoma(41) and melanoma,(44) does not involve insertion of an infusion pump.

The 2014 information summaries from the National Cancer Institute (NCI) state the following:

- Colon cancer
  - For patients with Stage 4 and recurrent colon cancer with liver metastases, hepatic intra-arterial chemotherapy with flouxuridine has had higher overall response rates but not a consistent improvement in survival when compared with systemic chemotherapy.(45)

- Primary liver cancer
  - For patients with localized and locally advanced unresectable adult primary liver cancer, infusion of chemotherapeutic agents with a subcutaneous portal or implantable pump via a catheter placed in the hepatic artery is described as a standard treatment option.(46)

Cancer Pain
Current NCCN guidelines (version 2.2014) for treatment of adult cancer pain recommend placement of epidural, intrathecal, or regional infusion pumps to deliver analgesic or anesthetic drugs as indicated.(47)
Noncancer Pain
Publications from the American Society of Interventional Pain Physicians include:

- Evidence-based guidelines (updated in 2009) on interventions for managing chronic spinal pain.\(^{(48)}\) The guidelines state that there is strong evidence to support the use of implantable intrathecal drug administration systems with proper patient selection criteria.

- A 2013 systematic review of intrathecal infusion systems for long-term management of chronic noncancer pain, as previously reviewed.\(^{(15)}\) The authors concluded that the evidence for intrathecal opioid infusion in this setting is limited. Intrathecal opioid therapy may be indicated in select patients, e.g., those with contraindications to oral opioid therapy.

Spasticity
In July 2012, Britain’s National Institute for Health and Care Excellence published an evidence-based clinical guideline on the management of spasticity in children and young people with nonprogressive brain disorders.\(^{(49)}\) Intrathecal baclofen may be considered for children and young people with spasticity or dystonia that causes difficulty with pain or muscle spasms; posture or function; or self-care or ease of care by parents or caregivers. Additional recommendations include:

- Consideration of potential adverse effects of reducing spasticity when spasticity may support function, e.g., by compensating for muscle weakness.

- A trial of intrathecal baclofen to assess efficacy and adverse events before deciding to implant the intrathecal pump.

In 2010, the European Working group for Spasticity in Children published a consensus statement on the use of intrathecal baclofen therapy in children with spasticity.\(^{(50)}\) For children with spasticity that interferes with function or quality of life, they recommended conservative treatment and a trial of oral medication before use of a pump to deliver intrathecal baclofen. They also recommended individuation of treatment and involvement of parents and caregivers. The group received an unrestricted educational grant from Medtronic (Minneapolis, MN).

U.S. Preventive Services Task Force Recommendations

The use of implantable infusion pumps is not a preventive service.

Summary

There is a large body of evidence on the use of infusion pumps, but the quality of the literature varies by condition. For patients with primary liver cancer, evidence is limited. However, these patients have few alternative treatment options, and some may benefit from hepatic arterial infusion of chemotherapy. Clinical input supported the use of implantable infusion pumps for this indication, which is therefore considered medically necessary.

For patients with colorectal cancer metastatic to the liver, a 2009 meta-analysis of randomized controlled trials found that hepatic arterial infusion of chemotherapy with implanted infusion pumps improves tumor control. For women with primary epithelial ovarian cancer, evidence from randomized controlled trials (RCTs) and a systematic review of RCTs indicates that an intraperitoneal infusion of chemotherapy can lead to improved survival and progression-free survival compared to intravenous chemotherapy only. Benefits of intraperitoneal chemotherapy must be weighed against the risk of
adverse events, which has been found to be higher with an intraperitoneal component of chemotherapy. For patients with chronic cancer pain, a systematic review of RCTs concluded that pain symptoms were reduced in patients who used an infusion pump. For these 3 indications, evidence is sufficient to conclude that the use of an implantable infusion pump improves outcomes and therefore may be considered medically necessary.

There is insufficient evidence suggesting that chemotherapy delivered through implantable infusion pumps improves health outcomes for patients with head and neck cancer or gastric cancer. Clinical input did not support use of this technology for these types of cancer. Thus, these indications are considered investigational.

For patients with intractable, non-cancer pain, the evidence consists of uncontrolled studies that report improvements in pain and quality of life following use of an implantable infusion pump. Additionally, guidelines from specialty societies support use of infusion pumps for this indication. For patients with severe spasticity, evidence from case series and non-randomized controlled studies reports improvements in symptoms, and there is support from specialty society guidelines for use in spasticity. Because of the strong rationale for use, the suggestive evidence, and the support from clinical guidelines, infusion pumps may be considered medically necessary for chronic, intractable non-cancer pain and for severe spasticity.

**Medicare National Coverage**

Medicare provides coverage for implantable infusion pumps for the following indications (31):

- Intra-arterial infusion of 5-FUdR (5-fluorouracil deoxyribose) for the treatment of liver cancer for patients with primary hepatocellular carcinoma or Duke's Class D colorectal cancer, in whom the metastases are limited to the liver and where the disease is unresectable or the patient refuses surgical excision of the tumor.

- Administration of anti-spasmodic drugs intrathecally (e.g., baclofen) to treat chronic intractable spasticity in patients who have proven unresponsive to less invasive medical therapy as determined by the following criteria:
  - As indicated by at least a 6-week trial, the patient cannot be maintained on noninvasive methods of spasm control, such as oral anti-spasmodic drugs, either because these methods fail to control adequately the spasticity or produce intolerable side effects, and
  - Prior to pump implantation, the patient must have responded favorably to a trial intrathecal dose of the anti-spasmodic drug.

- Administration of opioid drugs (e.g., morphine) intrathecally or epidurally for treatment of severe chronic intractable pain of malignant or nonmalignant origin in patients who have a life expectancy of at least 3 months and who have proven unresponsive to less invasive medical therapy as determined by the following criteria:
  - The patient's history must indicate that he/she would not respond adequately to non-invasive methods of pain control, such as systemic opioids (including attempts to eliminate physical and behavioral abnormalities that may cause an exaggerated reaction to pain); and
A preliminary trial of intraspinal opioid drug administration must be undertaken with a temporary intrathecal/epidural catheter to substantiate adequately acceptable pain relief and degree of side effects (including effects on the activities of daily living) and patient acceptance.

- Other uses of implanted infusion pumps if:
  - The drug is reasonable and necessary for the treatment of the individual patient;
  - It is medically necessary that the drug be administered by an implanted infusion pump; and
  - The FDA approved labeling for the pump must specify that the drug being administered and the purpose for which it is administered is an indicated use for the pump.

References


42. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology:
43. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology:
44. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology:
47. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology:
49. National Institute for Health and Care Excellence (NICE). Spasticity in children and young
people with non-progressive brain disorders: management of spasticity and co-existing motor
disorders and their early musculoskeletal complications, July 2012. Available online at:
50. Dan B, Motta F, Vles JS et al. Consensus on the appropriate use of intrathecal baclofen (ITB)
51. Centers for Medicare and Medicaid Services. Infusion pumps (280.14). Available online at:
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file
Deborah M. Smith, MD, MPH