Received: December 9, 2011 Revised: February 11, 2012 Accepted: February 14, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/j.1525-1403.2012.00449.x

# Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Granulomas (Inflammatory Masses)

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<Correction added after online publication 11 April 2012: The original version of this article contained incomplete and inaccurate author affiliations. The complete, corrected list of author affiliations is presented here.>

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**Introduction:** Continuous intrathecal infusion of drugs to treat chronic pain and spasticity has become a standard part of the algorithm of care. The use of opioids has been associated with noninfectious inflammatory masses at the tip of the intrathecal catheter, which can result in neurologic complications.

**Methods:** The Polyanalgesic Consensus Conference is a meeting of a group of well-published and experienced practitioners; the purpose of the meeting is to update the standard of care for intrathecal therapies to reflect current knowledge gleaned from literature and clinical experience. An exhaustive literature search was performed, and information from this search was provided to panel members. Analysis of the published literature was coupled with the clinical experience of panel participants to form recommendations regarding intrathecal inflammatory masses or granulomas.

**Results:** The panel has made recommendations for the prevention, diagnosis, and management of intrathecal granulomas.

**Conclusion:** The use of chronic infusions of intrathecal opioids is associated with the formation of inflammatory masses at the intrathecal catheter tip in a small minority of treated patients. Nonetheless, the appearance of these space-occupying lesions can lead to devastating neurologic sequelae. The prevention, early detection, and successful treatment of intraspinal granulomas are important considerations when offering intrathecal drug therapy to patients with chronic intractable pain.

**Keywords:** Chronic pain, consensus, granuloma, inflammatory mass, intrathecal

**Conflicts of Interest:** Timothy R. Deer, MD: consulting (Medtronic). Joshua Prager, MD: honoraria (Medtronic, Eli Lily, Qutenza). Robert Levy, MD, PhD: consulting (Medtronic and Codman & Shurtleff). Eric Buchser, MD: consulting (Medtronic). Allen Burton, MD: consulting (Medtronic, BSCIS, Stryker), speaking (Azur, Cadence, Cephalon, Neurogsx, Pricara, Pfizer), stockholder (Vapogenix). David Caraway, MD, PhD: consulting (Medtroinc, Spinal Modulation, MedSys, Codman). Michael Cousins, MD: nothing to disclose. José De Andrés, MD, PhD: nothing to disclose. Sudhir Diwan, MD: speaking (Neurotherm, BSCI). Michael Erdek, MD: nothing to disclose. Eric Grigsby, MD: clinical research (Alfred Mann Foundation, Medtronic, NeurogesX, Spinal Restoration), speaking (Azur Pharma), consulting (Medtronic, St. Jude Medical, Spinal Modulation, Vertos, Xalud), stock options (Spinal Modulation, Spinal Restoration, Vertos, Xalud). Marc Huntoon, MD, PhD: nothing to disclose. Marilyn Jacobs, PhD: consulting (Medtronic). Philip Kim, MD: consulting (Medtronic, Biotronik, Stryker, Azur). Krishna Kumar, MD: consulting and research (Medtronic, Boston Scientific). Michael Leong, MD: advisor (Covidien). Liong Liem, MD: grant (Spinal Modulation). Gladstone McDowell, MD: speaking (Azur), consulting (Medtronic, Mysys). Nagy Mekhail, MD, PhD: speaking (Endo Pharmaceutical), research (Baylis, Inc., Vertos). Sunil J. Panchal, MD: nothing to disclose. Richard Rauck, MD: research (Medtronic, Medasys, Azur, Codman, Al Mann Foundation), consulting (Medtronic, Medasys, Azur), data and safety monitoring board membership (Medtronic, Al Mann Foundation). Michael Saulino, MD, PhD: speaking (Medtronic, Azur), research (Medtronic). B. Todd Sitzman, MD: nothing to disclose. Peter Staats, MD: nothing to disclose. Michael Stanton-Hicks, MD: nothing to disclose. Lisa Stearns, MD: research (Medtronic, Insys Therapeutics, Vertos Medical), consulting (Medtronic). Mark Wallace, MD: research and consulting (Medtronic). K. Dean Willis, MD: speaking (Boston Scientific, Medtronic, St. Jude Medical), Implantable Systems Performance Registry participant (Medtronic), advisory committee (Boston Scientific). William Witt, MD: consulting (Medtronic), speaking (Cadence, Pfizer, Medtronic). Tony Yaksh, PhD: consulting (Vertex, Adynxx, Solace, Neuroadjuvants, Trevana), research (Adynxx, Johnson & Johnson, Xenome, Torrey Pines, Third Rock Ventures, Advanced Targeting Systems, Nektar Pharma, Endo Pharmaceuticals, Sage Rx, Solstice, Epigen).

## INTRODUCTION

Catheter-tip inflammatory masses (granulomas) have been observed after chronic intrathecal (IT) administration of a variety of analgesic agents. The first case of a catheter-tip granuloma associated with IT morphine infusion for the treatment of chronic intractable pain was reported by North et al. in 1991 (1). Granulomas have been characterized in large animals (e.g., dogs, sheep) and humans as distinct, globular, or spheroid collections of macrophages, plasma cells, eosinophils, or lymphocytes (2–8). They are aseptic (7), as defined by staining or culture, and almost always arise from the arachnoid layer of the meninges and not from neuronal tissue of the spinal parenchyma (2,7). Granulomas characteristically occur at the distal portion of the catheter (3).

Although granuloma formation is still thought to be an infrequent event in patients who undergo IT drug administration, reports of inflammatory masses are increasing. This increase may reflect the rising incidence of this potentially serious adverse event, as evidenced by postmarketing surveillance reports from Medtronic, Inc. (9,10), and by the increasing number of case reports and retrospective surveys of granuloma formation that have appeared in the literature since this phenomenon was first described (2,11–15). The seriousness of this adverse event is underscored by the finding that, among clinicians who have treated at least one patient with a granuloma, 66% reported having a patient who experienced permanent or temporary neurologic injury as a result of granuloma formation (12). The purpose of this communication is to further increase awareness on all of these clinical fronts.

The Polyanalgesic Consensus Conference (PACC) is a series of meetings convened by an expert panel of clinicians experienced with the use of IT analgesics for chronic pain management. This panel has published a series of consensus statements proposing ways to minimize the likelihood of granuloma formation. According to the 2000 consensus statement on the management of IT catheter-tip inflammatory masses (and an updated 2007 consensus statement on this topic), catheter-tip granuloma formation was associated exclusively with the use of IT opioid medications, both alone and in combination with nonopioid analgesics (5,16). Discontinuation of the offending IT medication in asymptomatic patients was recommended, with the expectation (based on previous clinical observations) that granuloma resolution would follow within two to five months (16). Indeed, results from magnetic resonance imaging (MRI) studies in canine models of IT morphine-evoked granulomas



  

demonstrated a significant time-dependent reduction in the size of the IT mass after discontinuation of morphine infusion (8). Thus, support for the maintenance of a low daily dose and low concentration of IT opioid medication, including morphine sulfate, in patients with no signs of granuloma was one key recommendation from the panel (16). The balance between avoiding granulomas and providing acceptable pain relief is often challenging and remains a significant problem in the successful management of this complex patient group.

In the 2007 consensus statement on the management of IT catheter-tip inflammatory masses (16), the PACC panel concluded that granulomas were associated with high doses or concentrations of opioid in the infusate, particularly when delivered over a long period; combinations of high drug concentration and slow cerebrospinal fluid (CSF) circulation rate; and intrathecally administered opioids (e.g., morphine). Generally, patients seek medical help after noticing new or worsening pain or the appearance of new focal neurologic abnormalities. Diagnosis can be difficult because most patients who experience these signs and symptoms do not have a granuloma; rather, they are experiencing progression of their underlying disease or escalating drug tolerance. Given the complexity of patient management and the difficulties in recognizing granuloma formation, expert guidelines might help to improve care. Indeed, members of the previous PACC panel issued a consensus statement in which they made key recommendations for prevention, screening, clinical assessment, and treatment relevant to IT granuloma formation in patients receiving IT drug therapy (16).

Granuloma occurrence in clinical practice has persisted, perhaps even increased, since the PACC last convened in 2007, and much new evidence related to the diagnosis and prevention of this condition has appeared in the scientific literature. Thus, the PACC reconvened in 2011 to modify and update their earlier recommendations regarding IT catheter-tip granuloma formation. The expert panel members reviewed previous PACC guidelines and recent reports of catheter-tip granulomas in the literature. The group also conducted a survey of physicians who routinely offer treatment with IT drug therapy. Consensus recommendations on critical issues related to IT catheter-tip granulomas were formulated.

### Methods

The present article is based on a review of previous PACC guidelines from conferences convened in 2000, 2003, and 2007 and includes data obtained from reports on IT catheter-tip granulomas that appeared in the medical literature between January 15, 2007, and March 1, 2011. These reports focused on the use of IT therapy for chronic pain. Databases searched included MEDLINE®, BioMed Central®, Current Contents Connect®, Embase™, International Pharmaceutical Abstracts®, and Web of Science®. Search terms included *morphine*, *fentanyl*, *sufentanil*, *methadone*, *adenosine*, *hydromorphone*, *meperidine*, *gabapentin*, *baclofen*, *ketorolac*, *midazolam*, *neostigmine*, *octreotide*, *ziconotide*, *ropivacaine*, *dexmedetomidine*, *clonidine*, *bupivacaine*, and *lidocaine*. These searches yielded 391 articles, which were evaluated for relevance to granulomas in IT therapy for chronic pain, yielding a total of 41 articles.

To find and evaluate data on MRI and IT granulomas, a separate literature search of Google Scholar and PubMed was performed with the use of the terms *intrathecal drug delivery*, *catheter*, *granuloma*, and *inflammatory mass*. Google was searched for images under the term *catheter tip granuloma*. Accessed internal bibliographies were also searched for content and additional references. Google was also used to search for recent relevant information regarding IT therapy for chronic pain, and additional literature considered by panel members to be relevant to this new consensus paper was reviewed. From these sources, 21 additional references were identified, for a total of 62 articles.

The literature search was limited by the potential inability to acquire accurate numerators from other sources on non-published cases, and may underestimate the actual incidence of granuloma. In future searches, the authors will consider sources such as FDA MedWatch and the MAUDE database to identify unpublished cases.

## LITERATURE REVIEW: SUMMARY OF CLINICAL AND PRECLINICAL DATA

### Overview

There are no data from controlled trials that document factors governing the formation of IT granulomas in patients receiving IT drug delivery for treatment of chronic pain. A single rigorous retrospective analysis was identified (13), as well as 12 case reports (2,17–26). Descriptive case reports are the primary sources of information about these granulomas.

### Epidemiology

More than 95,000 IT drug-delivery systems have been implanted worldwide since the 1980s, and the incidence of catheter-tip granuloma has generally been estimated at <3%, although estimates in select populations have been as high as 43% (27). Between 1990 and 2000, 41 cases of granuloma were reported through postmarketing surveillance to the US Food and Drug Administration (FDA) by Medtronic, Inc (9). Subsequently, from October 2000 through September 2007, Medtronic received reports of 448 granuloma cases in patients who had been implanted with drug infusion systems for treatment of pain (10). On the basis of the reports received by Medtronic through September 2007, the incidence of granuloma was estimated at 0.49% for patients ever implanted with a drug infusion system for the treatment of pain (10). Because patients receiving IT therapy have not routinely undergone imaging studies, the presence of a granuloma may be suspected only after clinical signs appear. However, occult granulomas that do not produce neurologic signs do occur (27); thus, the actual incidence of granuloma formation is likely higher than has been reported. The most recent analysis conducted by the pump manufacturer (Medtronic) indicates that the incidence of granuloma development is approximately five times higher (0.49%) than that originally reported in 2001 (0.1%), and the rate of detection of granulomas is expected to continue to increase (10).

According to results from an online survey that was developed to coincide with the 2007 PACC, 63.9% of physicians reported that at least one of their patients had developed a granuloma (12,13). In a retrospective analysis of hospital medical records, at a mean postimplantation follow-up time of 91 months (range, 9–209 months), 4 cases of IT granuloma occurred among 56 patients who received IT opioids, an incidence of 7% (13). In a retrospective cohort study with a three-year follow-up, ≥3.5% of 57 patients who received IT opioid therapy for chronic nonmalignant pain had a granuloma (11). A slightly lower rate of granuloma occurrence (3.0%) was reported for another cohort of patients ($N = 131$) receiving a continuous IT infusion of morphine (15).

### Granuloma Results from Actions of Opiods on Inflammatory or Mast-Cell Opiod Receptors

Results from pharmacologic investigations have indicated that the development of IT opioid-induced granulomas is not dependent on



  

opioid receptor activation (28). Instead, migration of inflammatory cells, most likely mast cells, from the local meningeal vasculature appears to be an important component of granuloma formation (28). The stimulus for this migration appears to be drug related, rather than related to a nonspecific effect of the catheter itself or the process of infusion, but the physiologic mechanism that drives cell migration remains unknown (7,23,28).

## Etiology

### Drug Dose

In current clinical practice, the dosage of opioid used for IT drug delivery is often increased gradually over the course of treatment because of tolerance, disease progression, or a new pain generator (2,19,20,23). It is common in clinical practice to increase the drug *concentration* as the daily dose of opioid is increased. The opioid concentrations needed often exceed the recommended limits (16,25,26). A correlation between opioid dose, yearly increase in opioid dose, and granuloma formation was demonstrated by Duarte et al. (13) in a rigorous retrospective analysis of 56 consecutive patients who received long-term IT drug therapy. In this study, a significant positive correlation was found between opioid (morphine or diamorphine) dose and granuloma formation ($r = 0.275$, $p < 0.05$). The mean $\pm$ standard deviation (SD) opioid dose for patients with a granuloma was 4.68 $\pm$ 1.55 mg/d (range, 3.79–7.00); for those patients without a granuloma, it was 3.01 $\pm$ 2.15 mg/d (range, 0.64–11.57; $p < 0.05$). There was a significant correlation between yearly increase of the morphine dose and granuloma formation ($r = 0.433$, $p < 0.01$); median opioid dose increase per year was 0.22 mg ($p < 0.005$) for patients with a granuloma. The mean $\pm$ SD annual change in dose was 0.88 $\pm$ 0.43 mg/d (range, 0.48–1.41) for patients with granuloma and 0.22 $\pm$ 0.19 mg/d (range, –0.08 to 0.97) for patients without granuloma ($p < 0.01$). It should be noted that some granulomas have been reported even in the setting of relatively low opioid concentrations. Thus, granuloma formation appears more likely in patients who are receiving higher opioid concentrations and in whom the rate of drug delivery is escalated more rapidly. This article is an example of an unusual presentation since diacetyl morphine was used during this study and is available in limited countries (UK).

Although a need for an increasing opioid dose may signal the development of a granuloma in some patients (13), there are case reports of opioids being titrated well beyond the recommended dosage limits (16) without the development of a granuloma (29). According to one report, 60 patients in a physician's practice had received high doses of IT opioids that were well beyond the recommended limits without the occurrence of a single catheter-tip granuloma (29). There appear to be some patient-specific characteristics that determine the propensity to develop these lesions, but such characteristics have yet to be identified.

### Drug Concentration

Extended tissue exposure to high concentrations of opioids such as morphine (>25 mg/mL) is believed to be an important factor in the development of catheter-tip granulomas (30–32). Results from a study in dogs showed that the morphine concentration of the infusate correlated with the local drug concentration near the catheter tip (8,28). Over a range of drug concentrations (i.e., 1.5–12.5 mg/mL) there was a strong correlation between the infusion drug concentration and drug concentration in the CSF at the sampling site within 2 to 3 cm of the infusion site. By assuming that the drug concentration precisely at the catheter tip corresponds to the infusion concentration, the authors determined that the local drug concentration (i.e., the steady-state drug concentration within the CSF) decreased 250- to 300-fold within 3 cm of the infusion site and that similar ratios were noted across a range of infusate drug concentrations. In this study, granulomas developed reliably with infusion drug concentrations of 12.5 mg/mL infused at 40 μL/h; under these conditions, the local drug concentration was 50 μg/mL. Granulomas were much less likely to develop at local drug concentrations less than 50 μg/mL. Extrapolating these animal data to clinical practice suggests that the use of an infusate with a lower drug (e.g., morphine, other opioids) concentration may reduce the likelihood of granuloma development in patients (20). It is interesting to note that the daily bolus delivery of a similar concentration of morphine in the dog did not produce a granuloma. This observation suggests that an ongoing exposure of the local meninges to analgesics via continuous infusion may be required for the accumulation of a mass of inflammatory cells. These findings raise the question of whether drug delivery by intermittent bolus may be safer than continuous infusion. No studies yet exist to compare the relative safety of these modes for drug delivery. In both human and canine studies, termination of the infusion leads to regression of the mass (8,20).

### CSF Flow Rate and Drug Distribution

Current biochemical and radiologic data do not support the existence of a consistent pattern of CSF flow to and from the cerebral ventricles and the lumbar cistern, and the dynamics of this process are controversial. Results from biochemical studies demonstrate a consistent and marked rostrocaudal concentration gradient for both the small metabolites (33) and the large protein constituents (34) of normal CSF. Radiologic findings obtained by using gated MRI demonstrate that CSF moves in a to-and-fro oscillation with respiration and the cardiac cycle (35), but there are conflicting data on the existence of bulk flow (36,37).

Direct evidence that CSF does not circulate has been obtained from preclinical studies in a porcine animal model (38). Limited rostral spread of IT opioid medications results in diffusion of much of the drug from the CSF to the epidural space, where it is absorbed into the systemic circulation. Consequently, much of the opioid dose placed within the IT space never reaches its intended target within the spinal cord. Results from these studies have demonstrated that drug distribution within the CSF and drug uptake (and dispersal) in the spinal cord (i.e., upon continuous IT injection at low-flow rates) may be limited to the region within a few centimeters of the catheter tip (39–41).

Mathematical modeling of fluid dynamics shows that, after IT dye injection, most dye is contained within the area directly adjacent to the catheter tip (30). Additionally, results from a study of chronic IT morphine delivery in a porcine model demonstrated a significant drug concentration gradient within the spinal cord as a function of distance from the infusion catheter tip. The authors suggested that the tendency for granuloma to form at the catheter tip may be related to a relatively high local drug concentration there (40).

The interpretation of the dye distribution analysis (30) and of the results from preclinical studies (8,40) is consistent with findings from a case report in which a granulomatous mass grew around a leak that had developed between an IT pump and the catheter (19). The granulomatous mass growing around the site of the leak provided a sealed conduit through which drug flow between the pump and the catheter had been reestablished. The authors suggested that growth of the granuloma at the site of the leak rather than at the catheter tip could be taken as evidence that the infused opioid had been the cause of the granulomatous lesion (19).

### Drug Flow Rate

The 2007 consensus statement on the management of IT catheter-tip inflammatory masses (16) indicated that granuloma formation



  

may be associated specifically with a high drug concentration and low drug administration flow rate. Although no association of a slow drug infusion rate and occurrence of granulomatous masses was found by Duarte et al. (13) in their retrospective study, the authors acknowledged that flow rate was not fixed; dosage changes were made by altering the flow rate of the infusate (i.e., with the use of a programmable pump), making it difficult to detect an effect of flow rate on granuloma formation (13). Further study of the impact of flow rate and the impact of localized CSF drug concentrations will be helpful in the design of new devices and novel agents for infusion.

Duration of Infusion

Cumulative risk for granuloma appears to be related to the length of time that the pump has been implanted (10). In patients who had pumps implanted for the treatment of pain, the incidence of granuloma occurrence over time since pump implantation showed a biphasic increase, first rising to a plateau after 2 years, then increasing once more at approximately 12 years, and remaining stable at that level at least for another 6 years (10). The reasons for this biphasic pattern are unknown.

**Drug Classes Implicated in Granuloma Formation**

Analysis of current data shows trends that can be used to educate physicians who are involved in the implantation of IT pumps. In addition to the use of morphine, other opioids are used in an off-label fashion. The clinician should consider whether these drugs may cause granuloma formation. In a review of the literature, we can evaluate the current data on the basis of FDA and manufacturer (Medtronic) reporting. The 2007 PACC panel provided specific guidance for doses and concentrations of IT opioids, including maximum concentrations and daily dose recommendations (see table 3 in Deer et al. 2008) (16). Somewhat different dosing and concentration guidelines have been provided in other review papers (42,43).

Granuloma formation has been consistently associated with the IT administration of opioids (e.g., morphine), either alone or in combination with other agents (13,17), as described in several case reports (Table 1) (2,17–26). In one case, a granuloma recurred twice in a single patient who had received IT morphine for approximately six years (23). After the first occurrence of a granuloma, IT morphine was resumed through a new catheter, and a new catheter-tip granuloma was identified five months later. Following surgical resection of the second granuloma, IT morphine therapy was again resumed, and a third catheter-tip granuloma was discovered three years later (23). One other case, in which a granuloma recurred within nine months of the surgical resection of the first granuloma, has been reported (17). These findings suggest the consideration of a conversion to an alternate opioid or nonopioid (e.g., ziconotide) in patients who have developed a granuloma with morphine and in whom IT therapy is still appropriate. If the clinician feels that the offending agent is still the best choice for treatment when considering the risk-to-benefit ratio, careful follow-up and high clinical suspicion for granuloma recurrence are recommended.

The development of a catheter-tip granuloma within the spinal cord parenchyma in a patient receiving long-term IT administration of morphine has also been described (2). A 54-year-old woman presented with an 18-year history of lower back pain, numbness from the waist down, and pain in her left leg, buttock, and groin. The patient had been receiving IT therapy for >9 years when progressive lower extremity weakness and urinary incontinence became markedly worse over the course of three weeks. An MRI study revealed a T2-weighted focal intramedullary enhancement of the left dorsal aspect of the spinal cord that was located adjacent to the catheter tip positioned near the arachnoid membrane; a 5-mm mass surrounded by edema that extended cephalad to the mid-T8 level and caudal to the level of T12-L1 was also noted. On surgical intervention, granulomatous material with scar tissue under the dura was observed, and a granuloma that had breached the pia mater through the dorsal aspect of the cord was present. This case of a granuloma of parenchymal origin is highly unusual because granulomas are commonly held to be meningeal in origin, and thus they generally arise from the dural and arachnoid layers, rather than from the pia matter or spinal cord (2). There was no evidence in this case that the mass had grown first and then penetrated into the spinal cord, since spinal tissue surrounding the small entry site was preserved (2). There was nothing unusual in the patient's medication or infusion history to suggest that these factors might be responsible for the manner in which the granuloma formed. The authors suggested that the granuloma may have been forced to grow within the spinal cord parenchyma because of a combination of factors: a thickened dura (which was not visible on MRI), the location of the catheter tip, and the particular characteristics of CSF flow (2). The theories presented by the authors cannot be confirmed because of lingering questions regarding potential causes of dural thickening, CSF flow relationship to the catheter tip, and any variations in CSF flow that may have occurred.

Results from preclinical studies in the canine model have shown that IT granulomas similar to those observed with morphine can be seen with other opioids, although some opioids are not associated with granulomas, even when used at relatively high concentrations/doses (28). In humans, catheter-tip granuloma formation has also been reported in association with the use of IT opioids other than morphine (Table 2) (29,44,45). In one such case, the patient had a confusing drug infusion history (44). She originally received IT opioid therapy but had inadequate pain reduction. The patient then received IT ziconotide monotherapy for approximately four months (44), but she again had an inadequate response and was switched to IT baclofen monotherapy; then, two months later, therapy was switched twice more to two other IT opioid medications administered as monotherapy. The patient subsequently developed a granuloma. This case is a good example of the complexity of determining the cause and effect of drug selection when analyzing this complication. The cause of the mass in this case was uncertain, and although the author suspected that the granuloma was opioid induced, no definite determination could be made (44). Additional cases of the association of IT catheter-tip granulomas with opioids other than morphine have been reported (14,45).

Several case reports associate hydromorphone use with IT granulomas (24,46). Coffey and Burchiel (46) described 41 patients with inflammatory masses who were identified from the literature ($N = 16$) or from Medtronic and FDA patient complaint databases ($N = 25$). All but two cases involved morphine ($N = 29$) or hydromorphone ($N = 10$) therapy. With both opioids, the inflammatory masses occurred over a wide variety of doses and concentrations. However, there is consensus that higher concentrations and doses increase the risk for inflammatory masses (16).

No cases of IT inflammatory masses associated with fentanyl or sufentanil have been reported (16,47). Results from animal model studies demonstrate that opioids have differing effects on inflammation and neurotoxicity (47). These models provide insight into mechanisms underlying causes of granuloma formation and differences in severity based on drug characteristics. Under experimental conditions, IT morphine has been shown to be the most aggressive inflammatory mass-causing agent, and these findings are consis-



  

**Table 1.** Recent Case Reports of the Occurrence of Intrathecal Catheter-Tip Granulomas With Morphine.

| Authors and year | Case description | Catheter tip placement | Time from pump placement to granuloma detection | Presenting signs/symptoms | MRI/CT findings | Surgical findings |
|---|---|---|---|---|---|---|
| Jourdain et al., 2009 (20) | 41-year-old man; intractable neuropathic pain; traumatic spinal cord injury; IT morphine for 3 months | T12-L1 | 5 weeks | Persistent pain | Mass visualized at catheter tip | NA |
| Hoederath et al., 2010 (17) | 52-year-old woman; history of chronic low back pain; IT morphine initially; switched to ziconotide and subsequently to another opioid | NA | 20 months (a second granuloma developed 9 months after surgical resection) | Increasing and persistent low back pain; onset of diffuse sensory deficits; hypoesthesia in the right lower extremity and in both feet | Intradural extra-medullary lesion at the level of T8-9; cord compression and contrast enhancement; second granuloma at T10-11 | Decompressive laminectomy revealed a 1 × 1 × 3-cm mass adherent to the spinal cord at the catheter tip |
| Jhas and Tuli, 2008 (2) | 54-year-old woman; 18-year history of lower back pain, numbness from the waist down and pain in her left leg, buttock, and groin; IT morphine analgesic admixture initially; switched to another opioid | NA | >9 years | Progressive lower extremity weakness markedly worse over the previous 3 weeks; left leg weakness; urinary incontinence | On MRI, a T2-weighted focal intramedullary enhancement of left dorsal aspect of cord adjacent to an arachnoid catheter tip; a 5-mm mass surrounded by edema extending cephalad to the mid-T8 level and caudal to the level of T12-L1 | Granulomatous material with scar tissue under the dura; granuloma breached the pia through the dorsal aspect of the cord |
| Leong et al., 2010 (22) | 68-year-old woman; previous lumbar surgery; IT morphine | T9-T10 | >7 years | Persistent thoracic spine pain; progressive lower limb weakness with paraesthesia, ataxia, constipation, and micturition difficulties | A 3.1 × 1.6 × 1.5-cm T1W and T2W isointense mass with marginal enhancement at the level of T9-T10; indentation of the thecal sac; moderate spinal cord compression; catheter tip seen in the posterior epidural space at T9-T10 | Decompressive laminectomy at the T9-T10 level; the catheter tip had migrated epidurally and was embedded in a large extradural fibrous mass |
| Leong et al., 2010 (22) | 39-year-old man; chronic pain from lumbar injury; IT morphine pump for 5 years | T12-L1 | >5 years | Progressive paraesthesia; lower limb weakness; foot drop; urinary incontinence; low bladder sensation; hyperreflexia in both limbs | A 2.0-cm × 1.0-cm T1W and T2W hypointense intradural mass; marginal cord compression at the level of T8 | Decompressive T8-T10 laminectomy; intradural calcified mass encasing the catheter tip |
| De Andrés et al., 2010 (23) | 60-year-old woman; motor neurologic deficit in lower limbs; poliovirus infection in childhood; IT morphine for 16 years, then switched to ziconotide | T9-T10 | 12 years, with recurrences 5 months later and 3 years after that | Progressive motor weakness; stabbing neuropathic pain in the lower limbs; increased local back pain, radicular pain, and hyperreflexia; loss of sensation | First intradural mass at T10; second and third masses at T11-T12 | Surgical removal of a mass of 1 × 1.4 cm and of a second mass of 0.8 × 0.5 cm |
| Webb et al., 2011 (19) | 38-year-old woman on chronic IT morphine/analgesic admixture; chronic gastrointestinal pain; Crohn's disease and diabetic gastroparesis | NA | 4 years | Decline in drug benefit 1 year before presentation; increased pain | Hub fracture observed on x-ray | Granulomatous structure noted surrounding the region of the pump nozzle |
| Abejón et al., 2009 (21) | Central neuropathic pain following removal of a tumor; long-term infusion of morphine | NA | NA | Gradual development of neurologic signs and symptoms suggesting radicular or spinal cord compression; steady increase in morphine dose | MRI images obtained | NA |
| Ramsey et al., 2008 (24) | 52-year old man; history of chronic lumbar pain; IT morphine for 6 years, then switched to another opioid | NA | 8 years | Increasing back pain, gait instability; recent-onset urinary retention and weakness in the lower extremities | Intradural-extramedullary lesion at the level of T8-T9 with cord compression | Decompressive laminectomy revealed a 1-cm mass adherent to the spinal cord adjacent to the catheter tip |
| Vadera, 2007 (25) | 47-year-old man; 3-week history of inability to ambulate or move his legs; multiple failed back surgeries for pain; IT morphine | T10-T11 | >4 years | Paralysis of both lower extremities and sudden increase in daily morphine requirements | Cord-compressing mass observed at the catheter tip | Laminectomy performed from T10-L1; a 1-cm intradural granuloma at T10 and T11 and at the catheter tip was noted; the mass was adherent to the spinal cord and involved the pia-arachnoid layer |
| Williams et al., 2011 (26) | 38-year-old woman; chronic thoracic spine pain related to T4 and T5 vertebral hemangiomas | NA | NA | Need for a high concentration and increased daily dose of morphine; decreased analgesia | Catheter-tip mass identified | Granulomatous mass removed |
| Sloan and Grider, 2010 (18) | 51-year-old woman; metastatic breast cancer to the spine; IT morphine | NA | <1 year | Rapid increase in daily dose of morphine; inadequate analgesia; severe, constant low back pain | Granuloma surrounding the catheter was apparent from a pump myelogram | NA |

MRI, magnetic resonance imaging; CT, computed tomography; NA, not available; IT, intrathecal; T1W, T1-weighted; T2W, T2-weighted.



  

**Table 2.** Case Reports of the Occurrence of Intrathecal Catheter-Tip Granulomas With Opioids Other Than Morphine.

| Authors and year | Case description | Catheter tip placement | Time from pump placement to granuloma detection | Presenting signs/symptoms related to granuloma | MRI/CT findings | Surgical findings |
|---|---|---|---|---|---|---|
| Gupta et al., 2010 (44) | 86-year-old woman; failed back surgery syndrome; pain localized to the lower lumbosacral spine; sequential IT ziconotide, baclofen, and nonmorphine opioid | T11 | 2 years | Lower extremity weakness, sensory changes, intractable lumbar pain | CT-myelogram confirmed the presence of a granuloma; identified a 4-mm epidural mass indenting the left anterior aspect of the dural sac and pushing the spinal cord | Surgery not recommended; IT medication replaced with normal saline |
| De Andrés et al., 2010 (45) | 61-year-old woman; morbid obesity, hypertension, and dyslipidemia; history of stroke without residual neurologic deficits; low back pain, lumbar canal stenosis | NA | 2.5 years | Numbness on the outside of the left lower limb; severe paraesthesia in the lower limbs; significant reduction in walking ability | Extramedullary, intradural, round mass (5 × 7 mm) at the T9 level; stenosis in the spinal canal | Dorsal laminectomy at T9 and T10; removal of a mass localized around the catheter |

MRI, magnetic resonance imaging; CT, computed tomography; IT, intrathecal; NA, not available.

**Table 3.** Case Reports of the Occurrence of Intrathecal Catheter-Tip Granuloma With Baclofen.

| Authors and year | Case description | Catheter tip placement | Time from pump placement to granuloma detection | Presenting signs/symptoms related to granuloma | MRI/CT findings | Surgical findings |
|---|---|---|---|---|---|---|
| Deer et al, 2007 (49) | 70-year-old man; right-sided weakness, atrophy, secondary spasticity of the upper and lower extremities secondary to a cerebrovascular accident | T10-T11 | 2.5 years | Dose requirements increased | Catheter tip at the T10-T11 interspace; space-occupying inflammatory mass at the catheter tip | NA |
| Deer et al, 2007 (49) | 39-year-old woman; progressive multiple sclerosis; permanent programmable IT pump | NA | 5 years | Worsening spasticity | Oval lesion consistent with an inflammatory mass identified | NA |

MRI, magnetic resonance imaging; CT, computed tomography; NA, not available; IT, intrathecal.

tent with clinical observations (8,16). Animal models with hydromorphone as the IT agent in both the dog and sheep model have shown the development of granuloma (48).

Two case reports of apparent granulomas associated with IT baclofen use have been described (Table 3) (49). In one case, the catheter tip was positioned at the T10-T11 interspace, and a space-occupying inflammatory mass was detected at the catheter tip via MRI. In the other case, an oval lesion consistent with an inflammatory mass was identified by MRI (49). The initial clinical presentation in both cases was reduced response to baclofen and increasing dose requirements.

Reevaluation of the MRI findings in these cases showed that they lacked the distinct globular- or spheroid-shaped lesions on T1 MRI sequences with gadolinium contrast that are considered diagnostic for histologically proven opioid-induced granulomas (50). Furthermore, in one of the cases, the patient who had severe and intractable spasticity had received a pharmacy-compounded IT baclofen preparation at a concentration of 4000 μg/mL, and the MRI scans in this case were similar to those obtained in a case in which a chalk-like precipitate had been found at the catheter tip (50). Notably, results of laboratory studies suggest that a pharmacy-compounded baclofen concentration of 4000 μg/mL is beyond the limit of drug solubility at physiological CSF osmolality and pH (51). It was therefore suggested that, in light of the preclinical and clinical findings, the reported data and images in these cases do not support a diagnosis of granuloma (50,52). In canine studies, the administration of baclofen at concentrations of up to 2000 μg/mL/d was not associated with the occurrence of any evident mass pathology (53). Since the mass in the patient who was receiving commercially available baclofen was equally problematic, the phenomenon cannot be attributed to compounding alone. Further analysis is needed should more of these lesions arise in other clinical settings. Granuloma formation associated with IT baclofen infusion, regardless of etiology, appears to be infrequent.

### Time for Development of Granuloma

According to one report of a retrospective analysis, the mean ± SD time for the development of granuloma is 39.5 ± 13.5 months (range, 22–52 months) (13). However, according to a variety of case reports, granulomas have been detected between 5 weeks (20) and 12 years (23) after the initiation of IT therapy (Table 1). In addition to



  

the case in which a granuloma was detected five weeks after initiation of IT therapy, other cases in which granulomas developed within one year have been reported (Table 1) (17,18,23). These case reports suggest that the formation of a granuloma is not strictly a long-term phenomenon. The time course over which a granuloma develops is likely to be underestimated because, in a clinical setting, the assessment of a granuloma depends on the appearance of neurologic signs, which may not be appreciated until well after the granuloma has actually begun to form. Asymptomatic lesions may exist for months or years before a clinical diagnosis is made or before symptoms and signs of clinical morbidity appear. Animal data suggest that granulomas can begin to form in days to weeks (8); the clinical implications of this finding are uncertain but may imply that, in some atypical patients, a course of early formation and potential clinical signs could arise. The acute models of animal studies have unknown implications for clinical practice.

**Catheter Position**

Catheter tips have been positioned at various thoracic levels, including T10, T11, and T12 (Tables 1 and 2) (20,22,23,25,44), as well as at cervical levels (20,22,23,25,44,54–57). No relationship between granuloma formation and catheter tip location has been identified to date. Support for previous theories that the low-flow state of CSF in the thoracic region may be responsible for an increase in granuloma formation has not been scientifically validated. The previous recommendations to keep the catheter below the conus do not appear to have any scientific support; no studies to date have shown that this practice will prevent neurologic sequelae, and some have theorized it may affect the efficacy of the therapy. Further study is needed to resolve these complex issues regarding catheter placement. It currently appears equally reasonable to argue in favor of placing the catheter at the level of the pain generator or in the lower thoracic spine or to support a placement below the conus to reduce the potential impact of mass compression on neural structures. Experts disagree, and no current consensus can be reached on the basis of scientific data.

**Clinical Signs and Symptoms of Granuloma**

The most frequently reported symptoms that lead to the diagnosis of a granuloma are decreased therapeutic response, inadequate pain relief, and onset of pain with new characteristics (e.g., increased local back pain, thoracic spine pain, gastrointestinal pain) (19,22,23,29). According to a report from Medtronic, Inc., decreased therapeutic response or inadequate pain relief and pain were reported in 33.5% of cases of IT therapy associated with a catheter-tip granuloma (10). Neurologic deficit or dysfunction accounted for another 17.4% of such cases (10). Other symptoms that have led to the diagnosis of granuloma include paralysis/paraplegia/paresis (15% of cases) and generalized weakness/muscle weakness (13.8% of cases) (2,22–24,29). Individual patient experiences that are consistent with the results of the aforementioned analysis are summarized in Table 1 (2,17,18,20,22,24).

**Radiologic Differential Diagnosis**

Because the number of patients with IT granulomas remains low in the population undergoing MRI scans, identification of such lesions with certainty may be difficult for radiologists, but any radiologist should be easily able to identify the presence of a mass. The radiographic appearance of these masses is easily confused with abscess or tumor. Thus, it is important that the radiology community include granuloma in the differential diagnosis for patients who are receiving IT therapy. In two case reports of patients who had symptoms of progressive spinal cord compression, features of catheter-tip granuloma included a thoracic spinal mass, central-low to intermediate T1-weighted and T2-weighted signal, a hypointense rim on both T1- and T2-weighted images, and relatively prominent regular border of enhancement on T1-weighted images taken after administration of gadolinium (22). In these reports, which describe typical MRI findings, the differential diagnosis of IT catheter-associated granuloma included progressive primary neurologic spinal cord disease, metastasis or infection, hemorrhagic ependymoma or hemangioblastoma with a secondary cord syrinx (because of cord hemorrhage), and intramedullary cavernoma. Addition of computed tomography (CT) allows for correlation between the position of the catheter tip and the location of the mass seen on MRI scan, thereby facilitating a presumptive diagnosis of granuloma. The diagnosis of catheter-tip granulomatous mass is confirmed by surgical resection in some cases, but more commonly the diagnosis remains unconfirmed because of the lack of need to resect the lesion when removing or replacing the catheter (19,22,24,25).

**Screening and Detection**

MRI with gadolinium contrast administration with thin slices at the catheter tip is the most common method for determining the presence of a catheter-related granuloma (16,29,58). According to results from a survey of IT practices, 94.3% of practitioners had used MRI to evaluate a suspected granuloma (12). MRI permits visualization of the soft tissue structures within the spinal canal (59) and can be used to define the size and location of any granulomatous lesion. Indeed, results from systematic studies in canines demonstrated a close covariance between size of the mass and the MRI image (8,28). In a letter to the editor of *Anesthesia & Analgesia*, Coffey and Allen (60) described catheter-tip inflammatory masses as usually "distinct, globular- or spheroid-shaped lesions best visualized on T1 MR image sequences with gadolinium contrast" and suggested that imaging diagnoses based on other criteria could be misleading. The authors included contrast-enhanced MRI scans of a catheter-tip inflammatory mass in a patient who was receiving morphine. In some cases an MRI is not possible because of contraindications. CT myelogram is an option in those cases and can be helpful in identifying lesions. Phillips et al. (61) presented three cases of IT catheter-tip granulomas and a report on imaging correlations between CT myelography and MRI. They also reviewed the literature on imaging appearance of granulomas in humans and animals.

In a report of three patients who were receiving IT therapy for pain, Blount et al. (62) described infusion complications due to granuloma formation. Magnetic resonance images indicated that all three lesions were relatively isointense with respect to the spinal cord on T1-weighted images and were hyperintense with a hypointense rim on T2-weighted images. The authors stated that IT contrast is necessary to differentiate inflammatory masses from the spinal cord.

It is important to be aware that a paramagnetic or metallic susceptibility artifact associated with MRI can distort the local tissue image and make it difficult to distinguish between a small mass around the catheter tip and an artifact caused by the metallic catheter tip itself in catheters with this feature (59). Failure to distinguish between the two can lead to unwarranted changes in therapy or unnecessary surgery. The imaging artifact is characterized by a central signal void appearing between two bright signals; the diam-



  

eter of the bright artifact is amplified 3.5-fold relative to the actual diameter of the catheter tip (59). Magill et al. (59) conducted a study that used three Medtronic catheter-tip models to characterize normal MRI image distortion produced by metallic IT catheter tips and differentiate that from catheter-tip granulomas. In an evaluation of patients with catheters in place, the authors provided images from MRI scans of those with and without granulomas and noted that granulomas enhanced after contrast administration, an important finding that suggests contrast should be used when indicated.

CT with myelography, a different imaging technique from MRI, can sometimes be used adjunctively with MRI to show a catheter more clearly than does MRI alone (22). This can be helpful in instances where metal artifact is present. More commonly, CT is used for patients in whom an MRI is not possible. According to results from a survey of IT practices, 43.4%, 7.5%, and 18.9% of practitioners had obtained a CT-myelogram, used CT, or performed a side-port study, respectively, to confirm granuloma formation (12). In using the side port to perform a CT-myelogram, care must be taken to aspirate CSF from the diagnostic port before administering contrast for myelography to avoid the potential for IT drug overdose caused by administering a bolus of concentrated drug that lies within the catheter between the side port and the CSF (29). Typical MRI and CT findings in patients with catheter-tip granulomas are described in Tables 1 through 3.

Miele et al. (3) provided another review of literature on catheter-related IT granulomas, which included a discussion of imaging.

It is important that the radiologists familiarize themselves with the subtle differences between artifact from metal catheter tips and granulomas. It is not possible or appropriate to expect the implanting doctor to educate the radiologist in this area and the panel recommends that radiologists who image patients in this population undergo proper training and continuing education.

### Treatment/Intervention

A variety of treatments and interventions for the management of granuloma have been proposed, many in the context of case reports. One option involves a nonsurgical approach in which drug delivery is either discontinued or replaced with saline infusion, allowing the granuloma to regress spontaneously (17,20). Another option is to replace the infusate with normal saline and leave the existing catheter in place while a new catheter is inserted for subsequent resumption of IT drug delivery. Indeed, the catheter-tip granulomatous mass often regresses spontaneously when the offending agent is removed from the area of the mass (20). In many cases, the physician may choose to remove the catheter and replace it with another catheter at a different IT level. This is often done when symptoms are bothersome, efficacy is not acceptable, or neurologic abnormalities are noted. Finally, fear of progressive neurologic injury may be a concern for cases in which spinal cord compression has occurred because of the presence of a granulomatous mass. In such cases, performance of a decompressive laminectomy with possible mass resection may be necessary (17,22). The catheter can be either removed (22) or reinserted (17) after surgical resection of the granuloma.

## DISCUSSIONS OF THE CONSENSUS PANEL

### Overview

The consensus panel reviewed and discussed options for the prevention, detection/diagnosis, and treatment of granuloma in patients receiving IT opioid therapy for pain. Discussions were focused on the recent published literature, the 2007 consensus statement on the management of IT catheter-tip granuloma, and the experience of the panel members.

### Patient Risk Stratification

Although the development of IT granulomas is infrequent, patients should be informed of the risks associated with IT therapy. Certain patients may be at greater risk of granuloma development. The panel noted that the following factors appear to place patients at higher risk for the development of granulomas: 1) administration of IT opioids of relatively high concentrations for any time period, although risk appears to increase with time; 2) a steady increase in the annual opioid dose, although this may be confounded by the consideration that increasing doses often lead to use of higher concentrations; 3) administration of high concentrations of IT drugs at low drug administration flow rates; 4) a history of granuloma formation; and 5) anatomic disease states that result in low flow of CSF around the catheter tip, such as severe cervical stenosis or traumatic spinal cord injury. A high index of suspicion for the development of granuloma is warranted in such high-risk patients. Published case reports provide little evidence of factors that identify patients as being at low risk for granuloma development. Granuloma formation can occur in patients who do not fit the high-risk profiles noted above.

### Prevention of Granuloma

Drug dose, drug concentration, method of IT administration, and duration of treatment continue to be the focus in prevention of granulomas, use of the lowest effective drug dose and concentration is recommended (10). Panel members indicated that bolus dosing as an adjunct to continuous infusion should be considered for IT drug administration as a way to limit the exposure of patients to opioid analgesics. By administering four to five boluses per day, the overall IT drug dose and the basal dose may be reduced. The total dose of opioid analgesics may also be reduced by the use of adjuvant therapy with nonopioid analgesics, thus theoretically lowering the patient's risk of developing a granuloma. Granuloma formation in association with lipophilic opioids appears to be rare, if it occurs at all; thus, the development of lipophilic drugs indicated for IT treatment of chronic pain may also lower the potential for these lesions.

#### Catheter Placement

Previous recommendations to place the tip of the intraspinal catheter in the lumbar thecal sac below the conus medullaris (10), whenever medically possible, in order to prevent severe and sometimes permanent neurologic consequences that may ensue once a granuloma develops have not been shown to be clinically preventive or helpful. The panel can recommend no ideal location for catheter placement to prevent granuloma formation. This concept is important because catheter placement in a location distant from the pain generator may result in higher dose and concentration requirements. On the basis of currently available data, the panel was able to make several conclusions about catheter placement: 1) granulomas can occur and cause significant neurologic injury no matter where catheters are positioned; 2) many experts feel that thoracic or cervical placement improves efficacy, but this has not been scientifically validated; 3) many practitioners continue to place all catheters at thoracic levels; and 4) many practitioners place all catheters below the conus. However, the panel cannot draw any firm conclusions about the best place to position catheters to maximize efficacy and minimize risks.



  

**Table 4.** Signs and Symptoms Associated With Granuloma.

- New or different sensory symptoms (e.g., numbness, tingling, burning, hyperesthesia, hyperalgesia, hypothesia, anesthesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurologic symptoms or signs that differ from baseline (e.g., reflex changes, clonus)
- Change in the character, quality, or intensity of pain
- The need for frequent or large escalations of the daily drug dose to maintain the analgesic effect
- Only temporary alleviation of increasing pain after rapid dose escalations
- Reports of new radicular pain, especially at or near the dermatomal level of the catheter tip

The placement of the catheter tip should be documented for future reference. If CSF flow is poor at the time of catheter placement, a myelogram study can be performed to quantify the level of flow. Such a study may help to determine whether there is a catheter obstruction that may cause the localized accumulation of a high concentration of analgesics at the infusion site. Catheter obstruction may be suspected if poor CSF flow is seen at the time of catheter placement, and it may be more likely in patients with a history of arachnoiditis. Myelographic studies carry significant risk, including allergy, inadvertent injection of a mismatched drug, and tissue injury due to injection. Therefore, such studies should be avoided in cases when flow is optimal.

**Screening, Detection, and Diagnosis**

Physicians who manage patients on IT therapy should remain vigilant in order to identify early clinical signs and symptoms of granuloma formation, especially when opioids are infused (10). Patients who are receiving IT therapy should be examined at each visit by a clinician familiar with the patient's baseline examination and details of the patient's spinal therapy. In the majority of cases, these examinations should occur at least every three months during the course of ongoing IT therapy. Not all home care agency personnel are qualified to adequately monitor patients receiving IT therapy. If the pump is being refilled by a home care nursing service, it is important that the patient be seen at least quarterly by the treating team, whenever possible.

If a granuloma is suspected, a careful patient history and neurologic examination should be completed. Signs and symptoms commonly associated with IT granulomas are listed in Table 4. If such signs and symptoms are reported, an imaging study should be obtained promptly to confirm or rule out granuloma (10). If a granuloma is detected, the following factors should be documented: 1) the location of the granulomatous mass in relation to the catheter tip; 2) type of implant used; 3) length of time since implantation; 4) daily drug dose (mg) and volume; 5) highest achieved drug concentration; 6) histopathologic analyses (if surgical resection is necessary); and 7) any confounding factors, such as occurrence of infection or tumors (16). The presence of either infection or tumor suggests that a granuloma is unlikely, and the identified disease should be treated, as appropriate.

The PACC 2012 panel members acknowledged that detecting granulomas by using imaging techniques could be challenging, as it may be difficult to distinguish between a granuloma and asymptomatic catheter-tip fibrosis.

**Table 5.** 2012 Recommendations: Prevention, Diagnosis, and Treatment of Catheter-Tip Granulomas.

Prevention

1. Use the lowest effective concentration and dose of IT opioid agents, especially of morphine sulfate.
2. Use bolus dosing instead of continuous infusion for IT drug administration.
3. Consider placing the tip of the intraspinal catheter in the lumbar thecal sac, below the conus medullaris.
4. Implement adjuvant therapy with nonopioid analgesics if concerned about granuloma formation.
5. Switch from IT opioid therapy to ziconotide if concerned about a recurrence of granuloma.

Screening/detection

1. Take patient history and perform physical examinations on patients receiving IT opioid or baclofen therapy at least every three months.
2. Routinely monitor patients receiving opioids or baclofen for prodromal clinical signs or symptoms of granuloma.
3. Monitor the yearly rate of increase in drug dose.
4. Educate clinicians and radiologists about the radiologic signs of granuloma.

MRI, magnetic resonance imaging; CT, computed tomography; IT, intrathecal.

MRI

For most patients, the imaging modality of choice for diagnosing granuloma is MRI. It is important that an MRI with contrast be used (if not contraindicated) because granulomas are more likely to be missed if MRI is performed without the use of contrast. Granulomatous lesions are relatively isointense in T1-weighted images in relation to the spinal cord (16). Additionally, T2-weighted scans that reveal a hyperintense image with a hypointense rim (or ring enhancement) could indicate the occurrence of either spinal cord compression or combined compression and local inflammation due to the presence of a granuloma (16). Although MRI remains the gold standard for detection and diagnosis of granuloma, routine use of MRI for screening purposes might not be cost-effective because granulomas occur with a low frequency. Therefore, costs associated with MRI must be considered when recommendations are made regarding the frequency of imaging tests. However, in the face of a neurologic deficit or unexplained increased pain, an MRI should be performed.

CT

In cases where an MRI is not readily available or is cost prohibitive, or for patients in whom MRI is contraindicated, a CT-myelogram can be used to detect IT catheter-tip granulomas. The procedure typically involves the injection of nonionic radiographic contrast through the pump side port or by a separate lumbar puncture below the level of the catheter entry site. To avoid complications or damage to the pump or catheter, contrast injection should be performed under fluoroscopic guidance with the use of the catheter access port kit (not the standard pump refill kit). If it is not possible to aspirate CSF from the access port, contrast should not be injected through the side port. The inability to aspirate CSF through the side port may be cause for concern but is not diagnostic for granuloma or catheter disruption. In such cases, a CT-myelogram with injection of the contrast directly into the CSF via a separate puncture is recommended.

2012 PACC Recommendations

Panel recommendations for the prevention of and screening for IT granulomas are presented in Table 5.



  

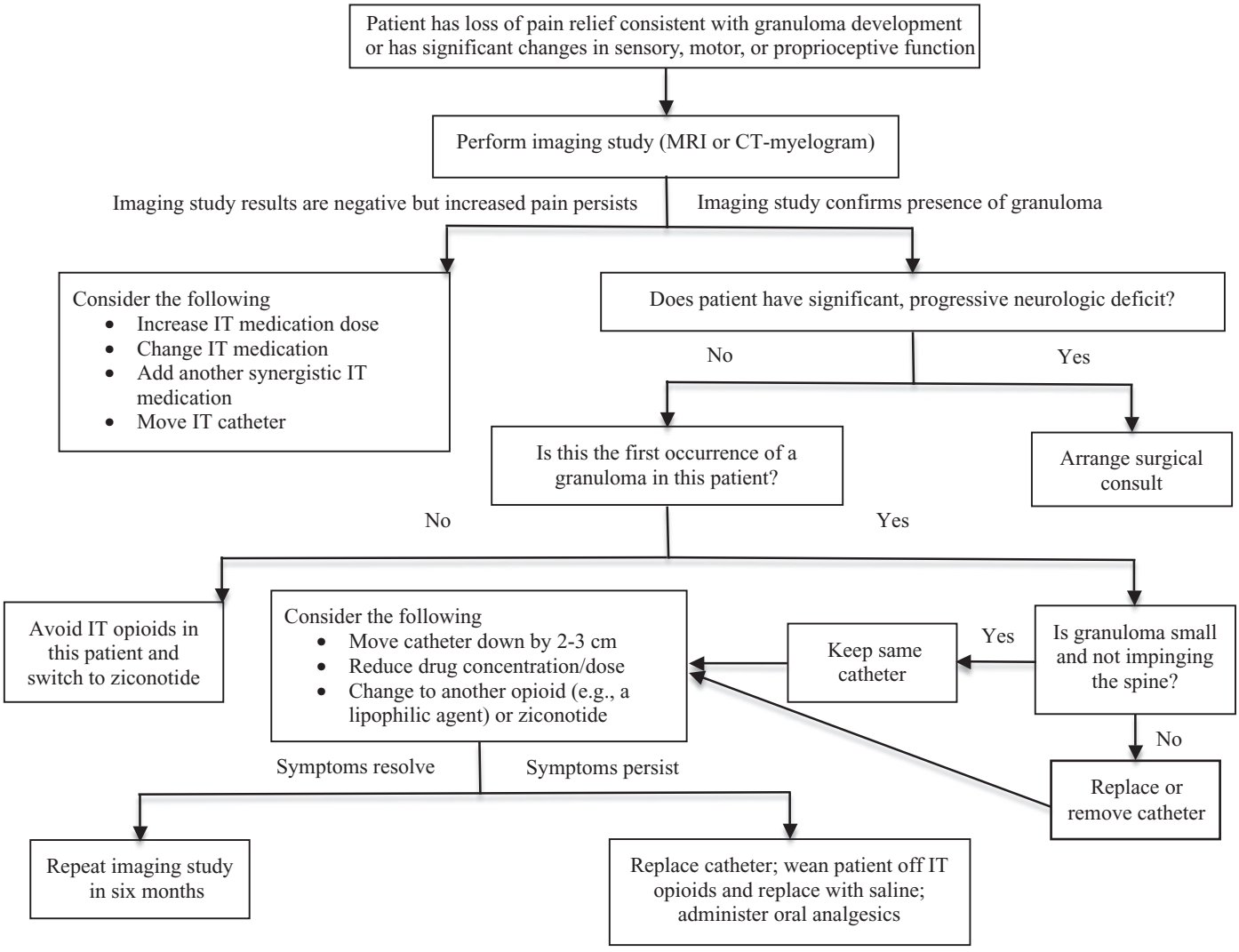


**Figure 1.** Algorithm for treatment of granuloma. MRI, magnetic resonance imaging; CT, computed tomography; IT, intrathecal.

**Treatment**

The treatment of granuloma depends on the urgency of the patient's clinical condition and the impact of the granuloma on neurologic function. Treatment decisions can vary depending on whether the patient is asymptomatic and has not experienced a change in pain level or the patient is symptomatic with neurologic impairment and a loss of drug efficacy.

Figure 1 shows the consensus treatment algorithm for IT granulomas. In patients who display signs or symptoms of a granuloma, an imaging study (MRI or CT-myelogram) should be performed. If the imaging study results are negative, but the signs/symptoms persist, an increase in the IT medication dose, a change in IT medication, or repositioning of the IT catheter should be considered. If the imaging study confirms the presence of a granuloma (Fig. 2), the treatment course depends, in part, on the patient's neurologic symptoms. If the patient has a significant, progressive neurologic deficit, prompt surgical removal of the granuloma should be considered after consultation with a neurosurgeon or orthopedic spine surgeon. If this is the patient's first granuloma occurrence, one of the following interventions are recommended (10): 1) reduction in the IT drug concentration, dose, or both; 2) switch to an alternate agent; 3) withdrawal of the catheter to a level 2 to 3 cm below the granuloma, a change that might result in a more beneficial drug

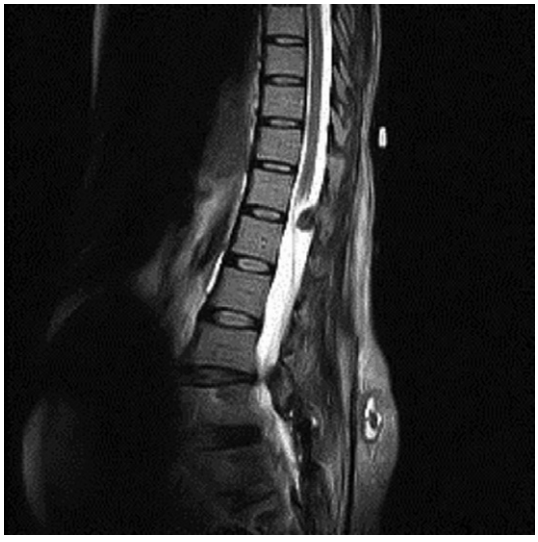

**Figure 2.** Granuloma at L1-L2 as seen on magnetic resonance imaging. <Correction added after online publication 11 April 2012: The original figure legend incorrectly identified the granuloma as appearing at T1-T2. The legend has been corrected here.>



  

distribution; or 4) removal of the catheter. In order to minimize surgical intervention, the distal catheter can be replaced and connected to the existing proximal catheter. This can be accomplished by removing the indwelling catheter by direct vision and retraction. The patient should be alert during removal to inform the implanter of any paresthesia. Paresthesia or resistance to removal should result in conversion to an open surgical removal at the time of the initial attempt or at a later date if the implanter does not have the ability to do a laminotomy or laminectomy and, as necessary, intradural and even microsurgical dissection. Forcibly removing the catheter can result in significant neurologic injury. Once the catheter is successfully removed, a new catheter is placed in the standard fashion with assurance of proper flow.

If, after the above steps are taken, the patient's signs and symptoms resolve, an imaging study should be repeated in six months. However, if signs and symptoms persist after the steps above are followed, the patient should be weaned off IT opioids, the pump should be filled with saline, and oral analgesics should be administered as needed until signs and symptoms resolve. Data exist to support the expectation that granulomas resolve with cessation of therapy and instillation of preservative-free saline (8).

### Conclusion

The occurrence of granuloma is now a well-recognized complication of IT drug delivery, and it should be suspected in certain clinical situations. The panel has recommended steps to reduce occurrence, improve identification, and modify treatment to improve overall long-term outcomes. Additional investigation is needed to further characterize the natural history of granuloma formation, more clearly define risk factors, and evaluate strategies for prevention and treatment.

## APPENDIX

### Survey Questions on Granuloma

In May 2011, three detailed surveys on IT infusion use, safety, and reimbursement were sent to more than 15,000 physicians and clinicians in the United States and internationally by the Polyanalgesic Consensus Committee. A total of 206 clinicians responded to the three detailed surveys. Of those respondents, approximately 55% were licensed anesthesiologists, 8% were physical medicine and rehabilitation physicians, and 7% were neurosurgeons. Nearly half of respondents (47.5%) were in private practice, 18% were in academic institutions, and 11% worked in private hospital systems. More than 55% of respondents had been working in pain management for longer than ten years. Seventy-five percent of respondents indicated that they dedicated at least 75% of their time to pain management in patient populations with an even distribution of neuropathic and nociceptive pain pathologies.

Among respondents, 34.6% denied ever having a patient develop a granuloma while under their care, 11.2% indicated they had had a single patient in their practice develop a granuloma, and 29% indicated they had seen between two and five patients with a granuloma. Of respondents who had seen at least one granuloma develop in their patient population, 38% noted that the granuloma(s) had developed while a programmable system was in use. Granuloma was confirmed via MRI 78.2% of the time; 32.3% of respondents indicated that they had confirmed granuloma via CT-myelogram, 12.3% via CT, and 23.0% via side port study (respondents were allowed to select more than one answer).

After confirmation of granuloma, 41.5% of respondents consulted a neurosurgeon, 40.0% removed and replaced the catheter, 26.1% repositioned the catheter, 13.8% left the catheter in place and merely changed the drug, and 9.2% completely removed the catheter (respondents were allowed to select more than one answer).

These survey responses may be a helpful reflection of clinical practice but may have the limitations of recall bias, low response rate (which might cause a biased selection of those on either end of the granuloma spectrum), and question bias due to survey creation flaws.

## Acknowledgements

Authors would also like to acknowledge the support provided by the International Neuromodulation Society, the staff at the Journal *Neuromodulation* for publication support; Audrey J. Suh, PharmD, for contributions to manuscript drafting and preparations; S. William Stuart, RPh; and Linda M. Page, PharmD, from Medtronic Neuromodulation.

**Special acknowledgement:** Christopher Bernards, MD.

**Sources of financial support:** This project was supported by grants from Medtronic, Inc. (Minneapolis, Minnesota, USA) and Azur Pharma Ltd (Dublin, Ireland).

## Authorship statement

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Drs. Timothy Deer, Joshua Prager, and Robert Levy chaired the project, led discussions, and garnered contributions from the consensus panel. Dr. James Rathmell performed a final review of the manuscript prior to final submission to the consensus panel for review and approval.

**How to Cite this Article:**

Deer T.R., Prager J., Levy R., Rathmell J., Buchser E., Burton A., Caraway D., Cousins M., De Andrés J., Diwan S., Erdek M., Grigsby E., Huntoon M., Jacobs M., Kim P., Kumar K., Leong M., Liem L., McDowell G., Panchal S., Rauck R., Saulino M., Sitzman B.T., Staats P., Stanton-Hicks M., Stearns L., Wallace M., Willis K.D., Witt W., Yaksh T., Mekhail N. 2012. Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Granulomas (Inflammatory Masses).
Neuromodulation 2012; 15: 483–496

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## COMMENTS

In the accompanying Polyanalgesic Consensus Conference (PACC) Report, Deer *et al*. update their previously published recommendations on the prevention, diagnosis and treatment of intrathecal catheter-tip granulomas. This is, by now, a well-known and feared complication of intrathecal opioid therapy. However, it occurs with sufficient rarity that it is difficult to synthesize this type of report in the absence of a group of experts. So, in the absence of an ability to resolve the issue with evidence-based means, the use of "eminence-based" recommendations such as this one is likely the next best option.

Intrathecal granulomas were first reported in the 1990's, and were initially felt to represent either indolent infections, or reactions to as-of-yet undescribed contaminants within the infusates. With time, however, and with a growing number of reports, certain common themes emerged: negative cultures, an association with intrathecal morphine, increased risk with high-dose/high-concentration drug, and a tendency to recur. Other reports have commented on all of these factors, but the number of reported cases has been low enough that it has been difficult to arrive at an accurate incidence of this complication or to synthesize a coherent recommendation for its prevention.

The Polyanalgesic Consensus Conference, composed of some of the most experienced implanters in the field, has previously made recommendations on the safety and efficacy of various intrathecal medications and their use in combination. PACC has also addressed the issue of catheter tip masses in the past, because of the importance of this topic in the neuromodulation community. PACC-2012 updates the recommendations of PACC-2007 on this topic by concentrating their review on studies published over the last 5 years, placed into context of prior knowledge. The more recent data appears to strengthen observations made in the previous PACC report: Catheter granulomas appear to occur exclusively with the use of opioids (most often morphine and its derivatives), and occur with greater frequency in patients treated with high doses, high concentrations and low-flow rates. And although there is as of yet no clear understanding of which factors (either drug- or patient-related) are crucial to the development of these masses, it is now well-accepted that patients undergoing chronic infusions of intrathecal opioids are at risk, and should be monitored.

Aside from strengthening the evidence on incidence and risk factors for granuloma development, this report is helpful in assessing, and ultimately debunking, claims on the development of these masses. For example, the report examines the claim that granulomas occur in the setting of baclofen infusion, finding that the few reports of this occurrence in the literature suggest either a mass not characteristic of a granuloma or a mass developing the setting of an unstably high concentration of the infused drug. The authors also address the important issue of the catheter tip placement, previously felt to be a factor in the development of neurological injury. At the time of the previous PACC report, many practitioners advocated placing the catheter tip below the level of the conus. In the present report, the authors examine the evidence and find that this practice pattern does NOT seem to reduce the risk of neurological injury with catheter-tip granulomas.

The authors of this PACC update on catheter-tip granulomas are to be congratulated for addressing an important issue that affects many in the pain neuromodulation community. The report is well-researched and thorough, and includes helpful decision algorithms. Physicians who use intrathecal pump therapy as part of their practice would do well to keep this reference close at hand.

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Comments not included in the Early View version of this paper.



  