Use of Intrathecal Baclofen in Children and Adolescents: Interdisciplinary Consensus Table 2013

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Note: This consensus statement has been acknowledged by the boards of the following societies:

- Gesellschaft für Neuropädiatrie (GNP, Society for Neuropediatrics) (S.B.)
- Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI, German Society of Anaesthesiology and Intensive Care Medicine) (M.K.H.)
- Deutsche Gesellschaft für Kinderchirugie (DGKCH, German Society for Paediatric Surgery (DGKCH) (L.B.)
- Arbeitsgemeinschaft Niedergelassener Neuropädiater (AG NPP, Working Party of Paediatric Neurologists in Private Practice) (S.A.)
- Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin (DGSPJ, German Society for Social Paediatrics (DGSPJ) (W.B.)

received
April 28, 2014
accepted after revision
June 23, 2014

DOI http://dx.doi.org/10.1055/s-0034-1387818.
ISSN 0174-304X.

Abstract

In recent years, intrathecal baclofen (ITB) has attained an important role in the treatment of severe spasticity and dystonia in children. There are principal differences between the use of ITB in children and its use in neurology and oncology in adults. Here, we present a consensus report on best practice for the treatment of severe spastic and dystonic movement disorders with ITB. Using a problem-orientated approach to integrate theories and methods, the consensus was developed by an interdisciplinary group of experienced ITB users and experts in the field of movement disorders involving 14 German centers. On the basis of the data pooled from more than 400 patients, the authors have summarized their experience and supporting evidence in tabular form to provide a concise, but still a comprehensive information base that represents our current understanding regarding ITB treatment options in children and adolescents.

Keywords
- intrathecal baclofen
- spasticity
- dystonia
- children

Introduction

Significance of Treatment with Intrathecal Baclofen

In recent years, intrathecal baclofen (ITB) has attained an important role in the interdisciplinary approach to treat severe spasticity and dystonia in children.

There are considerable differences between the various clinical centers within Germany with regard to the local setting and contributing specialist departments. Patients are looked after in departments and outpatient clinics for neuropediatrics as well as in so-called social pediatric centers, where interdisciplinary teams care for children with special needs. These centers are usually situated close to children's hospitals. Some pediatric neurorehabilitation specialty clinics are amongst the most experienced centers in Germany. Implantation of the pump system is usually the responsibility of the neurosurgery departments, rarely of the orthopedics or anesthesia departments. Looking after patients with pump implants in addition involves specialists in anesthesiology, pediatric intensive care, spinal surgery, and orthopedics. For some patients, effective palliative care requires an interdisciplinary approach. ITB centers should be able to draw on interdisciplinary cooperation between all specialist units involved (integrated approach). To date, there is neither a clinical guideline nor a uniform medical care concept for patients assigned to ITB treatment.

The use of ITB in children is licensed for children older than 4 years and requires obligatory prior testing with oral baclofen. In clinical practice, physicians are often confronted with situations where strictly following these criteria would not meet patients' needs. Some young children who are below the age of 4 years were presented with conditions requiring urgent treatment. In other patients, a delay of the initiation of therapy (e.g., for prior testing) would be to the disadvantage of the patient (see also section Aims of Consensus and Methods).

For application in children and adolescents, ITB is registered only for patients aged between 4 and 18 years suffering from severe chronic spasticity of cerebral or spinal origin (related to brain injury, multiple sclerosis, and spinal cord affections), under the provision that there is no response to orally administered antispastic agents (including oral baclofen) and/or that the effective oral dose leads to intolerable side effects (see Summary of Product Characteristics "Lioresal® intrathecal," January 2011).[1] Some of the indications and fields of application listed in this consensus table are outside the approved registration. In such cases, it is imperative to carefully explain the proposed treatment to parents or legal guardian and obtain their written informed consent for each individual patient. Treatment with ITB outside the constraints of the registered indications should not be withheld unethically. Such "off-label use" of drugs is common in pediatric practice for a range of different clinical conditions and drugs, and is categorized as individual "compassionate use" under the responsibility of the treating physician. Off-label-use of baclofen for the treatment of children and adolescents is based on current evidence from controlled studies as well as consensus recommendations published by national and international experts and medical societies.

Intrathecal application of baclofen requires specific experience and knowledge regarding correct indication, dosage, and application technique.

Table 1 Evidence levels and abbreviations

The level of evidence of clinical trials was rated level I–V according to AACPDM methodology to develop systematic reviews of treatment interventions, revision 1.2, 2008. The level of each clinical study is noted after the citation number.
• Level I: Systematic review of RCTs, large RCTs (with narrow confidence intervals; $n > 100$).
• Level II: Smaller RCTs (with wider confidence intervals; $n < 100$), systematic reviews of cohort studies, "Outcomes research" (very large ecological studies).
• Level III: Cohort studies (must have concurrent control group), systematic reviews of case–control studies.
• Level IV: Case series, cohort study without concurrent control group, case–control study.
• Level V: Expert opinion, case study or report; bench research, expert opinion based on theory or physiologic research, common sense/anecdotes.

Abbreviations: RCT, randomized controlled trial. AACPDM, American Academy for Cerebral Palsy and Developmental Medicine.

Table 2 Use of intrathecal baclofen—indications

Topic	Core statements	Selected literature
Muscular hypertonia originating from lesions of the brain	• Spasticity • Dystonia • Mixed forms • Applicable if hypertonia results in restrictions of activities/participation, communication, nutrition, general well being or care giving • Possible additive analgesic effects (data from animal experiments) • Possible indirect effects with influence on restlessness, sleep disturbances etc. • Cerebral palsy: GMFCS III-V	Proof of principle: [5]/V, [6]/3 Reviews: [7]/R, [8]/R, [9]/R, [10]/R European consensus statement: [2]/C Evidence-based reviews: [3]/III, [11]/III Clinical studies on spasticity or mixed forms of hypertonia originating from lesions of the brain: [12]/IV, [13]/IV[a], [14]/IV, [15]/IV, [16]/IV, [17]/IV, [18]/IV, [19]/IV[a], [20]/IV, [21]/II, [22]/II, [23]/IV, [24]/R, [25]/IV, [26]/IV, [27]/IV, [28]/IV, [29]/V, [30]/IV, [31]/IV, [32]/IV, [33]/IV, [34]/III, [35]/IV, [36]/IV, [37]/IV
Spasticity due to lesions of the spinal cord	• Less common ITB indication in children compared with adults • Because of trauma, infection, postinflammatory reaction, tumor, or malformation • Hereditary spastic spinal paralysis as a rare and difficult to treat condition • Difficult to balance between desired reduction of muscle tone and undesirable muscle weakness.	Spinal cord lesions: [38]/V, [39]/IV
Early rehabilitation	• Cerebral hypoxia, traumatic brain injury and others • In the early phase: autonomic dysregulation • In the early phase: ITB may allow to reduce medication that may interfere with reorganization/rehabilitation (e.g., benzodiazepines) • Early and late phases: avoid spasticity, contractures and malalignment of joints • Despite ITB treatment, children with traumatic brain injury have a better outcome compared with children with hypoxic brain injury	Early rehabilitation: [40]/IV, [41]/IV, [42]/IV
Progressive encephalo (myelo) pathy	• Palliative, that is, the primary goal is to control symptoms for improved well being	Progressive neurological disorder: [43]/III, [44]/V
Dystonias	• Lower level of evidence compared with spasticity • Dyt-1-negative dystonia • Nonresponders to pallidal stimulation	Clinical studies dystonia: [30]/IV, [31]/IV, [45]/V, [46]/IV, [47]/V, [48]/V Status dystonicus: [49]/V
Ambulant patients and upper limb function	• Difficult to balance between reduction of spasticity and loss of muscle force.	ITB in ambulant children: [50]/IV, [51]/IV, [52]/III, [53]/IV Upper limb function: [46]/IV
Off-label use	Patient age less than 4 y constitutes off-label use but is not per se a contraindication. Use of ITB is indicated, e.g., after cerebral hypoxia, but also for all other disorders with muscular hypertonia or autonomic dysregulation resistant to other forms of treatment.	

Table 2 (*Continued*)

Topic	Core statements	Selected literature

Factors that might limit the treatment response to ITB	• Fixed malposition of limbs and/or spine
	• Paresis and plegia
	• Severe dystonia, "dystonic storms"
	• Hyperkinetic-choreiform movement disorders
	  • Unfavorable effect/side effects ratio
	  • Dystrophy, impaired wound healing
	  • Behavioral disorders
	  • Unreliable patient care due to family situation/caregivers/distance to experienced clinical centers
	  • In isolated cases, but not generally, epilepsy (see the section Side Effects and Troubleshooting)	

Abbreviation: C, consensus statement; ITB, intrathecal baclofen; R, nonsystematic review.
Note: For details on levels of evidence, please refer to ►**Table 1**.
[a]Placebo vs. ITB during test phase.

Aims of Consensus and Methods

The range of neuropediatric disorders for which treatment with ITB is indicated, as well as the practical approach clearly differs from applications in adult neurology and oncology. This calls for a thorough work-up of the topic with regard to the specific requirements in pediatrics. The consensus presented here aims to (1) summarize and evaluate the available studies (focusing on clinical studies in humans with an emphasis on children and adolescents) in terms of evidence-based medicine and (2) describe the practical approach in German-speaking treatment centers (practice-based evidence). The methodology of rating clinical trials is outlined in ►**Table 1**. We explicitly have included off-label indications. The aim of this study is to present the full range of current practical experience. Because of its complexity and adaptation to individual patient needs, it is impossible to present recommendations for ITB treatment that would be universally applicable to each individual patient and situation. The introductory text (10 sections) and the 10 consensus tables are intended to provide orientation and allow the reader to become familiar with the current range of applications and practical approaches. The authors hope that the tables will be a valuable source of information for all physicians and therapists involved in treating children and adolescents with movement disorders.

On the basis of the available literature (key words: intrathecal baclofen; database: PubMed; last search: October 2013) with special consideration of the European consensus on this form of therapy,[2] the systematic review on the treatment of spasticity in children and adolescents with cerebral palsy,[3] and the European consensus on the treatment with botulinum toxin,[4] the authors developed the consensus table presented here during regular meetings of the ITB working party. This group as a whole represents the experience with approximately 450 ITB treatments acquired over a period of more than 15 years. The proportion of children younger than 4 years varies between centers from 0 to 30%.

Indications

In principal, indications for treatment with ITB include severe spasticity of spinal or cerebral origin, and severe dystonia uncontrollable with oral medication. Accordingly, there is a broad range of disorders that can be considered for treatment with ITB.

It has to be acknowledged that the vast majority of clinical studies with ITB including the studies with the highest evidence level investigated patients with primarily spastic movement disorders. For patients with severe dystonia, evidence for this treatment intervention is much less, and the treatment effect and its significance in daily life of the patient are much more difficult to predict.

Before establishing an indication, the treating physician should (1) clarify the underlying etiology of the movement disorder, (2) classify the movement disorder (spasticity, dystonia, other forms of hypertonia, degree of severity, and distribution pattern) using suitable assessment tools, and (3) specify any comorbidities that might potentially aggravate spasticity. For details of indications and supporting references, please refer to ►**Table 2**.

Selection of Patients

Classification of patients with cerebral palsy (and correspondingly of many patients with other movement disorders) using the Gross Motor Function Classification System (GMFCS) has proven useful because a patient's classification grade (I–III vs. IV/V) is of central importance when deciding on achievable therapeutic goals for this patient. Data on the efficacy of ITB mostly relate to patients classified as GMFCS grades IV and V. In those patients, therapy primarily aims at the functional level to reduce spasticity and at the activity level to improve general well being, reduce pain, and facilitate patient care and everyday activities, acknowledged as important aspects for quality of life. Thus, ITB essentially relieves symptoms for a range of disorders but has no influence on the

Table 3 Use of intrathecal baclofen—selection of patients

Topic	Core statements	Selected literature
Clarify etiology of the disorder	Classification of movement disorders and comorbidities • Dystonia versus spasticity • Grade of severity (GMFCS and MACS) • Epilepsy, communication, behavioral disorder etc. • Nutritional state • Neuro-orthopedic findings (limbs and spine)	GMFCS: [54,55]
Consider and clarify comorbidities that may contribute to reduced wellbeing or aggravate hypertonia	• Raised intracranial pressure • Obstipation • Neurogenic bladder, urinary tract infections/pyelonephritis • Other infections • Hip joint luxation • Osteoporosis and fractures • Scoliosis • Pain originating from other causes • Gastroesophageal reflux • Epilepsy and nonconvulsive status • Behavior	Comorbidities: [25]/IV, [56]/IV
Treatment goals (see the section Evaluation)	• Realistic, relevant, and precise • ITB only, if time and effort versus benefit analysis favors treatment • Mutually agreeable team decision on treatment (parents or caregiver, the treating therapists and physicians at home as well as in the ITB center)	
Anticipatory measures to assure adequate patient care	• Who will be responsible for taking care of the patient in reasonable vicinity to his or her place of living and who decides on continuing, changing, or ceasing treatment? • Before treatment with ITB, prepare for any required aids (e.g., corset and sitting support) including counseling, prescription, and clarifying how costs are covered. • Consider the optimal sequence of ITB, neuro-orthopedic or spinal surgery	Scoliosis, orthopedic surgery: [57]/IV, [58]/IV, [59]/IV
Context	• Understanding, dependable, and supportive caregivers/parents • Access to a physician with special expertise in baclofen treatment • Written informed consent	Patient information brochure [German language]: [60]/P

Abbreviations: GMFCS, gross motor function classification system; ITB, intrathecal baclofen; MACS, Manual Ability Classification System; P, patient information leaflet.
Note: For details on levels of evidence, please refer to ►**Table 1**.

underlying pathogenesis. ITB decreases muscle tone but can at the same time also aggravate paresis and has no influence on other symptoms of the upper motor neuron syndrome. Improved mobility of the patient is only rarely achieved. Generally, treatment with ITB is carried on for years. Exemptions are cases of early rehabilitation where ITB may be used at an early stage for several months up to a few years for symptom control of autonomic dysregulation and severe spasticity or dystonia. Detailed information is provided in ►**Table 3**.

Treatment with ITB is elaborate and complex. A critical consideration of time, effort, and risk versus benefits is necessary. For effective and safe therapy it is essential to put down in writing clearly outlined treatment goals and how and when during the course of therapy evaluations should be done. Other prerequisites are reliable caregivers, competent

Table 4 Use of intrathecal baclofen—testing

Topic	Core statements	Selected literature
Testing to check for allergic reactions	As explained in the Summary of Product Information for baclofen, appropriate tests are required to reveal any risk of allergic and potentially anaphylactic reactions before pump implantation. We recommend prior testing with orally administered baclofen.	Summary of product characteristics of intrathecally administered baclofen[1]
Arguments pro testing	• Allows to assess what effect on hypertonia can be reasonably expected • Evaluation of tolerability • Helps to gain acceptance of ITB from parents and caregivers.	Testing before implantation: [21]/II, [22]/II, [30]/IV, [8]/R
Arguments against testing	• The limited time frame of testing does not provide sufficient information for reliable prediction of long-term therapeutic outcome • Risk of infection • Time delay: when testing via catheter, pump implantation has to be delayed by at least 4 weeks to reduce risk of infection. (Note: some centers implant the pump immediately after testing via external catheter). • Testing via external pump may lead to a higher rate of complications after subsequent pump implantation.	
Evaluation and monitoring during testing	• Efficacy: Muscle tone, proprioceptive reflex, well being and patient care • Side effects: Closely monitor blood pressure. There is a risk of arterial hypotonia because of reduced venous blood flow due to lowered muscle tone in the leg muscles and central vasodepression. Monitor respiratory frequency, heart rate, and state of consciousness (see also the section Side Effects and Troubleshooting).	H-reflex and flexor reflex utility and feasibility: [29]/V, [61]/II
Tests with single bolus injection (single or multiple application(s) via lumbar puncture or external catheter)	• Appropriate in spasticity • Appropriate in cooperative patients able to communicate how treatment effects them • Lumbar puncture: use only short-acting analgesics and sedation (administered i.v.) to enable clear differentiation between the effects of analgosedation and baclofen. • Preparation: Baclofen for intrathecal use, concentration of 0.05 mg/mL • Initial dose 25–50 µg, mixed with spinal fluid during application • Onset of action after injection: Start: 30–90 min, Maximum: 3–4 h, Duration: 8–24 h • If the observed effect is unsatisfactory,	Single bolus injections: [7]/R, [8]/R, [62]/IV Technical note on ultrasound guidance: [63]/IV

(*Continued*)

Table 4 (*Continued*)

Topic	Core statements	Selected literature
	repeat testing after 24 h with increased dose. Increase by 25–50 µg. Do not exceed a total of 100 µg.	
Testing with continual administration (spinal catheter and external pump)	• Appropriate especially in dystonia • Preparation: 10 mg/20 mL. If daily dose > 300 µg: 10 mg/5 mL. Which preparation is suitable depends also on the type of external pump. • Strictly observe sterile conditions when filling the external pump. • Initial dose: Max. 100 µg/d. Incremental dose increases: 50 µg/d • Duration of test: as short as possible, as long as necessary, usually 2–14 d, if justified in special cases up to 21 d. • Prophylactic treatment with antibiotics to reduce risk of infection (controversial issue) • Closely monitor vital functions and state of consciousness. • Subcutaneous tunneling and use of a small-gauge catheter minimize risks of infection and leakage.	Testing continuous: [30]/IV, [64]/IV
ITB treatment without prior testing	• On the basis of the clinical picture and after careful consideration of the pros and cons of alternatives (see the section Integrative Therapy), ITB seems the only promising treatment option. Testing would unduly delay the indicated early start of treatment. • Example 1: Early rehabilitation after hypoxic brain injury • Example 2: Patient with severe dystonic cerebral palsy or progressive encephalopathy, and proven resistance to alternative treatment options (see the section Integrative Therapy) • Example 3: Severe dystonia with scoliosis that makes positioning the test catheter especially challenging and thus pose increased risks for the patient and impinge on final catheter positioning	Implantation in early rehabilitation without testing: [40]/IV, [42]/IV

Abbreviations: ITB, intrathecal baclofen; i.v., intravenous; R, nonsystematic review.
Note: For details on levels of evidence, please refer to ►**Table 1**.

medical and therapeutic aftercare within reasonable distance from the patients' place of living.

While treatment of patients younger than 4 years constitutes off-label use, such a young age is not per se a contraindication. ITB is justified for children younger than 4 years after cerebral hypoxia but also in all other disorders associated with muscular hypertonia resistant to therapy by any other means. Over the years, this group of authors has accumulated experience in the treatment of more than 75 such patients.

Contrary to the Summary of Product Characteristics of baclofen[1] treatment with ITB after traumatic brain injury should be considered not only "when spasticity has stabilized (i.e., at least 1 year after injury)" but already when generalized spasticity is developing and is affecting the course of rehabilitation.

Epilepsies, including difficult to treat epilepsies, are not per se contraindicate for treatment with ITB. The pros and cons, that is, the need for treating the hypertonia versus the risk of aggravating epileptic seizures, have to be carefully

weighed against each other, taking into account that ITB may improve the patient's well being and sleep and thereby positively influence epilepsy.

We wish to point out that parents and any other family members and caregivers must be comprehensively informed about the mode of action, technique of administration, and possible adverse side effects. Caregivers must be able to recognize any side effects or complications of therapy. Therefore, clear and precise information is indispensable. The consensus group has prepared a comprehensive information brochure.[60]

Testing

For testing before final pump implantation, patients should be admitted to a specialized center with adequate experience. The testing phase should be performed in an inpatient setting under close supervision by appropriately qualified specialists. Prior oral baclofen to test tolerability is mandatory.

ITB is administered either via lumbar puncture or via a spinal catheter. The purpose of the test is to detect any intolerance and to assess the effect on muscle tone, rather than predicting final overall efficacy.

Vials of 50 µg/mL baclofen are available for bolus testing. The initial dose for puncture is 25 to 50 µg. The onset of action occurs after approximately 30 to 90 minutes and the maximum effect is reached after approximately 4 hours. The effect lasts 8 to 24 hours. Therefore, to reduce the risk of adverse effects, a second testing with double the initial dose should not be done earlier than 24 hours after the previous injection. As a general rule, the bolus dose should not exceed 100 µg.

In cases where it is difficult to predict the clinical outcome and its effect on the patient's everyday life, the test injection should be done via a spinal catheter. To reduce the risk of infection, the catheter should be tunneled under the skin for approximately 3 cm from the actual puncture site. Baclofen may be administered in the form of repeated

Table 5 Use of intrathecal baclofen—dose

Topic	Core statements	Selected literature
Prediction of response from oral medication	Nonresponse to oral baclofen does not allow reliable predictions as to the effect of intrathecal application. Although the intrathecal dose is 100–1,000-fold lower than the oral dose, efficacy is higher.	
Available baclofen solutions for intrathecal application	• 10 mg/5 mL and 10 mg/20 mL (Note: These two solutions have different baclofen concentrations, namely, 2 and 0.5 mg/mL). Other volumes/concentrations might enter the market in the future. Strictly avoid confusion. • Use the lower concentration for low doses (if required dilute further with isotonic saline solution).	
Dosage (responsibility is with the treating physician. Deviations from what is suggested is possible in selected cases)	• Specified in µg/d • Determined individually for each patient with consideration of effect and side effects of treatment. • Body weight is irrelevant for dose calculation • Determination of baclofen levels in body fluids is redundant, since it cannot be measured in blood and levels in spinal fluid do not correlate to clinical efficacy • "Usual" dosage: 100–2,000 µg/d • Initial dose: 50–100 µg/d • Acceptable dose changes during inpatient stay/postoperative: 50 µg/d or 10–20% of the daily dose, maximally in 100 µg increments • Acceptable dose changes in outpatient care: 25 µg/d or maximally 10% of the daily dose • Electronically controlled pumps can be programmed also for pulsed or circadian baclofen delivery—an option worth trying in cases of unsatisfactory baclofen action.	Dosage: [12]/IV, [17]/IV, [2]/II, [26]/IV, [29]/V, [52]/III, [74,75] Pulsatile bolus applications: [18]/IV, [76]/IV, [77]

Note: For details on levels of evidence, please refer to ►**Table 1**.

bolus injections or continuously injected over several days using an external pump. When testing was done via a spinal catheter, implantation of the final pump should be done after an interval of at least 4 to 6 weeks after removal of the catheter.

In some patients, prior testing may be omitted if the indication can be clearly established and the course of action well justified. Details on methodology of testing can be found in ►**Table 4**.

Implantation

In children, the pump is always placed in an abdominal pouch under general anesthesia. A gastric tube does not constitute a contraindication but should always be planned ahead of pump implantation. The pump is implanted subcutaneously, or subfascially. Positioning of the catheter tip may vary depending on the underlying problems. In lower limbs accentuated tetraplegia, some authors recommend to place the tip at Th10–Th12, in tetraplegia at C5–Th2, and in generalized dystonia at C1–C4. Other authors do not see any differences in drug efficacy between different catheter positions and routinely place the tip in the middle to upper thoracic region. Some aspects of implantation procedure are outlined in ►**Supplementary Table S1**[65–73](online-only).

Dose

Baclofen is a GABA-B agonist. The muscle-relaxing effect is primarily due to an increase of presynaptic inhibition at the spinal level and thus a reduction of mono- and polysynaptic reflex transmission. Intrathecal administration, bypassing the blood–brain barrier, allows 100- to 1,000-fold lower doses than those used in oral administration. Nevertheless, the possibility of central effects cannot be ruled out (see section Side Effects and Troubleshooting).

There is no definite correlation between the baclofen concentration in cerebrospinal fluid and the clinical effect. It therefore makes little sense to measure drug concentration in cerebrospinal fluid. The most suitable dosage has to be determined individually and for each patient based on the observed therapeutic efficacy. Specifics on dosage can be found in ►**Table 5**.

Postimplantation Phase, Aftercare

Straight after pump implantation, the dose should be adjusted while closely monitoring the patient. This is best done while the patient still remains in hospital but in exceptional care situations also may be done in an outpatient setting. In parallel, a reduction of oral antispastic medication should be attempted.

ITB may lead to deterioration of trunk control. Accelerated progression of scoliosis during treatment with ITB has been described and controversially discussed in the literature. We recommend regular clinical and radiological checkup in 3 to 6 months' intervals. Further parameters to be regularly reviewed are as follows: Progress toward therapeutic goals, use of aids and orthoses, and indications for combination with other treatment options (e.g., botulinum toxin, orthopedic interventions, etc.).

Control of pump function, fill-up of the pump reservoir, and dose adjustments during the course of treatment may be done in the outpatient unit by appropriately trained physicians. Refill intervals depend on the reservoir volume of the pump and the administered dosage, and are generally between 2 and 6 months. Longer intervals should be avoided because the solution in the pump may become unstable. If using high doses, shorter refill intervals as far down as every 3 weeks may be required. Details are provided in **Supplementary Table S2**[78–82](online-only).

Side Effects and Troubleshooting

As with all surgical interventions, perioperative complications may occur already during pump implantation but are altogether rare. Because of comorbidities, particular attention should be given to the anesthesiologic risk.

Patient and caregivers as well as physicians and therapists treating the patient should be alerted to a possible dysfunction of the implanted system. If symptoms of a patient raise suspicion, we recommend to successively check for any deficiencies, such as, incorrect catheter positioning or leakage, and to take immediate corrective action. We highly recommend close cooperation between conservatively and operatively treating physicians, such as pediatric neurologist and neurosurgeon. Pump pouch and catheter are prone to microbial contamination. Special care should be taken to maintain aseptic conditions when refilling the pump. Side effects of ITB are primarily dose dependent. Overdosing can occur especially during test and dose adjustment phases. In addition, errors in pump programming or confusion of drug concentrations should be considered as a possible source for overdosing. Frequently observed symptoms are as follows: Pronounced muscular hypotonia, arterial hypotension, tiredness, headaches, dizziness, urinary retention, nausea, and vomiting. Overdosing may lead to impaired consciousness and respiratory insufficiency requiring artificial respiration. The best counteraction is to treat the patient symptomatically in the intensive care unit and to initiate a stepwise and intermittent reduction of baclofen supply (beware of withdrawal symptoms!). The authors do not consider drawing of cerebrospinal fluid with the aim to lower the baclofen concentration in CSF, or parenteral administration of physostigmine as a suitable means for treating overdose symptoms.

ITB may cause a reduced bowel movements and thereby intestinal obstruction. During test and dose adjustment phases, therefore, micturition and bowel function should be carefully monitored and persistently treated if symptoms appear.

Withdrawal symptoms typically appear as a result of malfunctions in the catheter system, a too low level of the infusion solution in the pump reservoir or a too low battery level. The withdrawal symptoms are as follows: Increasing muscle tone, restlessness, vomiting, insomnia, confusion, pruritus, and finally convulsions up to the point of multiorgan failure. Relevant aspects of this important topic are highlighted in ►**Table 6**.

Table 6 Use of intrathecal baclofen—side effects and trouble shooting

Topic	Core statements	Selected literature
Allergy/anaphylaxis	Refer to the section Testing	Summary of product characteristics[1]
Side effects	• Dose dependent • Often observed during test phase and postoperative adjustment phase • Reversible, partly only intermittent until adjustments are completed • Usually avoidable by using low initial followed by slowly increasing doses • Typical symptoms: Muscular hypotonia, arterial hypotension, feeling tired, convulsions, headaches, nausea, micturition, feeling sick, vomiting, obstipation, intestinal obstruction	Side effects: [17]/IV, [23]/IV, [25]/III, [26]/IV, [40]/IV, [83]/IV, [84]/IV, [85]/IV, [86]/IV, [87]/IV, [88]/IV, [89]/V, [90]/IV, [91]/IV, [92]/IV, [93]/IV, [94]/III, [95]/IV
Infections	• If the condition of a patient with pump implant deteriorates consider a possible microbial contamination of pump pouch or catheter system. Regular check for bacterial contamination of the residual baclofen solution retrieved from the pump during refill procedure is not recommended.	Infections: [85]/IV, [96]/IV, [97]/IV
Overdosage/ intoxication	• Typical symptoms: Nystagmus, breathing depression, flush, arterial hypotension, impaired consciousness, and convulsions • Symptoms appear unexpectedly and acute: Consider errors in programming, confusion of available infusion solutions, inadvertent subcutaneous injection during refilling • To do: Admit patient to the intensive care unit for continuous monitoring and treatment of symptoms • Reduce baclofen dosage. Beware of withdrawal symptoms.	Overdose: [18]/IV, [98]/V, [99]/C, [100]/V, [101]/V, [102]/V, [103]/IV
Withdrawal symptoms	• Usually appear as a result of faulty function in the implanted system • Occurs with an incidence of 16–30%, depending on the level of experience with ITB treatment in the treating center • Symptoms: Increasing muscle tone, feeling restless, vomiting, insomnia, clouded consciousness, pruritus, convulsions, multiorgan failure	Withdrawal: [14]/IV, [8]/IV, [80]/III, [83]/IV, [88]/R, [92]/IV, [100]/V, [103]/IV, [104]/IV, [105]/R, [106]/V, [107]/R, [108]/V, [109]/V, [110]/IV, [111]/IV, [112]/V
Possible causes of withdrawal symptoms	• The pump–catheter or catheter–catheter connection came undone; dislocation • A kink in the catheter or some other defect • Faulty pump function • Empty reservoir/incorrect filling of the pump • Expired battery	Imaging evaluation of ITB systems: [80]/R, [81,113]/V, [114]/V Intraventricular vs. Intrathecal catheter placement: [72]/IV, [71]/IV
How to manage withdrawal symptoms	• Intensive-care monitoring and treatment • Sedate with, e.g., benzodiazepine and apply oral baclofen as a transient measure • System check: Puncture the side port, aspirate spinal fluid. Administer contrast agent. X-ray after cranial and caudal tilting; use computed tomography to assess epidural distribution of the contrast agent, and MRI to assess a possible involvement of granuloma at the catheter tip. Each site supplying patients with ITB should follow a detailed scheme how to check for dysfunction	
ITB and epilepsy	• The Summary of Product Characteristics states that baclofen must not be used in treatment-resistant epilepsy • In isolated cases, aggravation of epilepsy has been observed during ITB treatment • Evaluate pros and cons: Epilepsy is a frequent comorbidity in children with symptoms indicated for treatment with ITB. The severity of those symptoms may justify treatment with ITB even in the presence of treatment-resistant epilepsy.	Epilepsy: [84]/IV, [87]/IV, [115]/III

Abbreviations: C, consensus statement; ITB, intrathecal baclofen; MRI, magnetic resonance imaging; R, nonsystematic review.
Note: For details on levels of evidence and expansions of abbreviations, please refer to ►**Table 1**.

Integrative Therapy

ITB treatment should be seen as a treatment option within a comprehensive treatment concept for severe spasticity and dystonia. A treatment graph for children with cerebral palsy that illustrates reasonable combinations has been developed.[116] Details are provided within **Supplementary Table S3** (online-only).

ITB often has a more pronounced effect on proximal rather than distal muscle groups. In this situation, patients often benefit from concomitant treatment with botulinum toxin. To date, only few studies are available on the efficacy of treatment combinations.

Evaluation

Outcome evaluation with standard procedures for muscle tone and joint range of motion such as the modified Ashworth scale or Tardieu scale are important but not sufficient to adequately depict treatment outcome. Standardized video documentation can provide helpful additional information. More important is the evaluation of individual treatment goals, for example, with Goal Attainment Scaling or with the Canadian Occupational Performance Measure. Evaluation of the patient's well being with instruments, such as CPCHILD, provides further relevant information. A list of suitable evaluation instruments can be found in ►**Table 7**.

Table 7 Use of intrathecal baclofen—evaluation

Topic	Core statements	Selected literature
General recommendations	• Treatment with ITB is primarily used in children and adolescents with severe health problems. Many of the standardized evaluation tools are therefore not suitable or only applicable with restrictions. • Most important is the evaluation of treatment outcome based on the treatment goals defined before starting treatment. If necessary, these goals may have to be redefined during the course of treatment. Clearly, the quality of evaluation will benefit if the patient is seen by the same treating physician(s) and physiotherapist(s) throughout the entire treatment period. • The European Consensus on the Treatment with Botulinum Toxin provides evaluation tools that may be suitable for less severely afflicted patients. • The items below are listed in accordance with the International Classification of Functioning, Disability and Health and focus on children of GMFCS levels IV/V. No claim is made as to completeness of this list.	Consensus statement botulinum toxin: [4]/C Evaluation: [16]/IV, [20,32]/IV, [33]/IV, [37]/IV, [117]/IV, [118,119]/III, [120]
Body structure/ body function:	• (modified) Ashworth Scale • (modified) Tardieu Scale • Joint range of motion according to the neutral null method • Video documentation • Barry Albright Scale • Burke–Fahn–Marsden Dystonia Rating Scale • Goal Attainment Scale • Canadian Occupational Performance Measure (COPM)	
Activity/ participation:	• Video documentation • Gross Motor Function Measure • WeeFIM (Functional Independence Measure) • Pediatric Evaluation of Disability Inventory • Canadian Occupational Performance Measure • Goal Attainment Scale • Child Health Questionnaire • Visual Analogue Scale • Pain scales • Caregiver Priorities & Child Health Index of Life with Disabilities	German translation CPCHILD: [121]

Abbreviations: C, consensus statement; GMFCS, gross motor function classification system; ITB, intrathecal baclofen.
Note: For details on levels of evidence, please refer to ►**Table 1**.

Table 8 Use of intrathecal baclofen—documentation

Topic	Core statements	Selected literature
Information is mandatory	Clear documentation of the treatment with intrathecal baclofen is important, especially with regard to the patient's safety. Several cases reported in the literature illustrate how information deficits hampered timely recognition of adverse events. According to the German Medical Devices Act, each patient must receive a written information for patients' document at initiation of the treatment.	Legal text in Germany: §10 MP BetreibV

Information about treatment details	• Issue each patient with an appropriately completed treatment identification card. Ask the patient to present this card at each visit for updating.
	• Each baclofen pump comes with a written information for patients' document that should be handed over and explained to the patient.
	• The medical report should include and highlight the following information:
	  • Pump type
	  • Pump volume
	  • Type and concentration of the drug
	  • Dose per day
	  • Date to which the reservoir alarm is set
	  • Date for the next refill	

Information about possible side effects	The medical report should also draw attention to the possibility of inadvertent drug overdosing or withdrawal and describe the associated symptoms. Furthermore, the medical report should specify contact persons and a phone number through which a specialist is always within reach.	

Documentation

With implantation of a medical device, the treating physician is obliged to provide parents or the legal guardian with a clearly written patient information document which usually comes along with the pump implanted.

Primarily for the benefit of the patient's safety, clear documentation of the implanted device, dosage, refill interval, and battery status has a high priority. Some suggestions can be found in ►**Table 8**.

Disclosures

The contents of the consensus table and agreement between authors were developed during annual meetings of the working party. Medtronic GmbH, Meerbusch, Germany, kindly provided financial support toward participants' travel and accommodation costs. Participants received no other support or financial allowance from any manufacturer of drug infusion pumps or pharmaceutical companies. This article was developed and written by the authors without any influence or contribution by Medtronic or any other third party.

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