

# Invasive Treatments for Complex Regional Pain Syndrome in Children and Adolescents

## *A Scoping Review*

Boris Zernikow, M.D., Ph.D., Julia Wager, Ph.D., Hannah Brehmer, M.D., Gerrit Hirschfeld, Ph.D., Christoph Maier, M.D., Ph.D.

### ABSTRACT

This review aimed to synthesize the current evidence on the effectiveness of invasive treatments for complex regional pain syndrome in children and adolescents. Studies on children and adolescents with complex regional pain syndrome that evaluated the effects of invasive treatment were identified in PubMed (search March 2013). Thirty-six studies met the inclusion criteria. Articles reported on a total of 173 children and adolescents with complex regional pain syndrome. Generally, many studies lack methodological quality. The invasive treatments applied most often were singular sympathetic blocks, followed by epidural catheters and continuous sympathetic blocks. Rarely, spinal cord stimulation and pain-directed surgeries were reported. An individual patient frequently received more than one invasive procedure. Concerning outcome, for approximately all patients, an improvement in pain and functional disability was reported. However, these outcomes were seldom assessed with validated tools. In conclusion, the evidence level for invasive therapies in the treatment of complex regional pain syndrome in children and adolescents is weak. (**ANESTHESIOLOGY 2015; 122:699-707**)

**C**OMPLEX regional pain syndrome (CRPS) remains a diagnostic and therapeutic challenge. Due to the lack of knowledge regarding its exact pathophysiology, reliable diagnostic tests are not available. When CRPS is diagnosed, it always bears some uncertainty because the diagnosis depends solely on observable signs and reported symptoms, which have been consolidated into various diagnostic criteria sets.<sup>1-3</sup> An individual patient may be diagnosed with CRPS if one diagnostic criteria set is used but not if a different one is used.<sup>4</sup> Uncertainty also exists regarding therapy. Myriad different therapies have been applied to patients with CRPS with questionable benefits. Most therapies have been tried in an uncontrolled manner in small samples that were not well defined or in single individual patients only. The Cochrane Library contains three CRPS-related reviews. Those reviews do not recommend local anesthetic sympathetic blockade, cervico-thoracic or lumbar sympathectomy, or spinal cord stimulation (SCS) for chronic pain in adult patients with CRPS due to insufficient evidence.<sup>5-7</sup> The CRPS dilemma

extends to prognosis, which also remains speculative for the individual patient.

Complex regional pain syndrome mainly affects adults but it is reported in the literature that it affects children from the age of 2.5 yr.<sup>8</sup> The uncertainty regarding the diagnosis, therapy, and outcomes of CRPS is even more substantial in children or adolescents compared with adults.<sup>9</sup> In childhood, the clinical appearance of CRPS seems to differ from that in adults with more pediatric patients having no detectable prior physical trauma or operation and more adolescents having cool, cyanotic extremities.<sup>9,10</sup> Sensitivity and specificity of the standard diagnostic criteria sets have not been analyzed for pediatric patients. The prognosis of CRPS in children is uncertain.<sup>9</sup> Although short-term outcome seems promising with a resolution of functional disability in 70 to 90% of the patients,<sup>11,12</sup> the one work investigating long-term prognosis reports less favorable outcomes<sup>13</sup>: after a median follow-up of 12 yr, 52% of the former childhood patients with CRPS had current pain; 57% had pain that increased with movement;

This article is featured in "This Month in Anesthesiology," page 1A. The figures were prepared by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

Submitted for publication June 12, 2014. Accepted for publication October 27, 2014. From the Department of Children's Pain Therapy and Paediatric Palliative Care, Witten/Herdecke University, School of Medicine, Witten, Germany (B.Z., J.W.); German Paediatric Pain Centre, Children's Hospital, Datteln, Germany (B.Z., J.W., H.B., G.H.); University of Applied Sciences, Osnabrück, Germany (G.H.); and Department of Pain Management, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Ruhr University Bochum, Bochum, Germany (C.M.).

Copyright © 2014, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2015; 122:699-707

and 45% had skin temperature changes or a limited range of motion.<sup>13</sup> There is an ongoing debate about the role of psychological factors and psychological trauma in the development and aggravation of childhood CRPS.<sup>14,15</sup>

Despite the uncertainty regarding the pathophysiology, diagnosis and therapy in adult CRPS, and the differences between adulthood and pediatric CRPS, invasive therapies are applied in children and adolescents. Therefore, we aimed to perform a scoping review of the evidence for invasive treatment approaches in pediatric CRPS regarding study quality, kind of treatment, and outcome.

## Materials and Methods

### Literature Search

The initial PubMed search (conducted on March 28, 2013; no time limit) used two combined groups of keywords. The first set of keywords referred to CRPS; as the terminology for CRPS changed in recent years, we also included synonyms for CRPS in our queries (search term ["complex regional pain syndrome" OR "CRPS" OR "reflex sympathetic dystrophy" OR "Morbus Sudeck" OR "Sudeck's atrophy" OR "causalgia" OR "algodystrophy"]). The second search term referred to pediatric samples (search term ["children" OR "pediatric" OR "child"]). The initial search led to 323 results whose abstracts were screened for inclusion. Twelve additional articles were identified by checking references cited by full-text articles assessed for eligibility.

### Inclusion Criteria

The title and the abstract of all 335 articles identified were reviewed by three independent reviewers (G.H., H.B., and J.W.). Discrepancies were resolved by discussion.

To be included, articles had to fulfill the following criteria specified in advance:

1. studied patients who were diagnosed clinically with CRPS
2. included pediatric patients (age range, 0 to 18 yr)
3. reported on invasive treatment delivered by the authors
4. reported original empirical data
5. written in English or German

Overall, 36 of the 335 screened articles met the inclusion criteria. Their full texts were retrieved for further analysis (fig. 1).

### Data Extraction

A data extraction sheet was developed. To minimize potential bias, all data were extracted by two independent raters (H.B. or J.W. and B.Z.). Discrepancies were resolved by discussion.

The following information was retrieved: (1) quality criteria of the studies including information on the study design, methods, and reporting standards; (2) study details including the type of study, patient characteristics, and CRPS

diagnosis criteria; (3) treatment including prior and concurrent conservative interventions and invasive treatment; and (4) outcomes including changes in pain parameters, edema, functional disability, emotional distress, and harm (relapse, infection, or death). Methods of the data analysis were specified in advance.

## Results

### Overview of Included Studies

A total of 36 publications published between 1972 and 2013 have been included in the review. Most studies were case reports and case series (n = 33; 92%). Nineteen articles were single-patient case reports, and 14 articles reported on a group of children and adolescents with CRPS (case series). Data on 110 patients were presented in these case reports and case series. In addition to these studies, two controlled studies (n = 40 patients)<sup>16,17</sup> and one randomized control trial (n = 23 patients)<sup>18</sup> were identified. They included a total of 63 patients. Of these studies, 25 articles reported on invasive and noninvasive therapies for pediatric CRPS, whereas the remaining studies focused exclusively on invasive interventions. A total of two articles (6%) addressed invasive therapies for a mixed adult and pediatric population.<sup>17,19</sup>

### Patients

The articles comprised a total of 173 patients, predominantly girls (weighted mean, 83%). The median average age calculated on the basis of 32 studies was 12 yr (range of average age, 8 to 15 yr; weighted mean, 13.2 yr). Table 1 provides an overview of the patient characteristics.

### Study Quality

Only a minority of the studies used a firm diagnostic criteria set for the CRPS diagnoses. One case series (n = 2 patients)<sup>20</sup> and the randomized controlled trial (n = 23 patients)<sup>18</sup> applied the CRPS diagnostic criteria proposed by the International Association for the Study of Pain.<sup>1</sup> One case series (n = 4 patients)<sup>21</sup> used the Budapest clinical criteria.<sup>2</sup> No articles used the Veldman<sup>3</sup> or Budapest research criteria.<sup>2</sup> The remaining studies (n = 144 patients) reported symptoms of CRPS without applying well-established or any formal diagnostic criteria sets. Of those studies, 21 were published after the publication of the first official criteria set—International Association for the Study of Pain taxonomy—in 1994<sup>1</sup>.

Although sample characteristics and interventions were usually described carefully, outcome measures were only described in a few studies (table 2). Only half of the publications reported the length of follow-up. The median of the average follow-up was 6 months (weighted mean, 2.9 months). The length of follow-up ranged from 0.7<sup>19</sup> to 96 months.<sup>22</sup>

### Treatment before Invasive Procedures

Prior treatment was reported in 26 publications (72%). Specifically, 19 publications (53%) reported on physiotherapy.

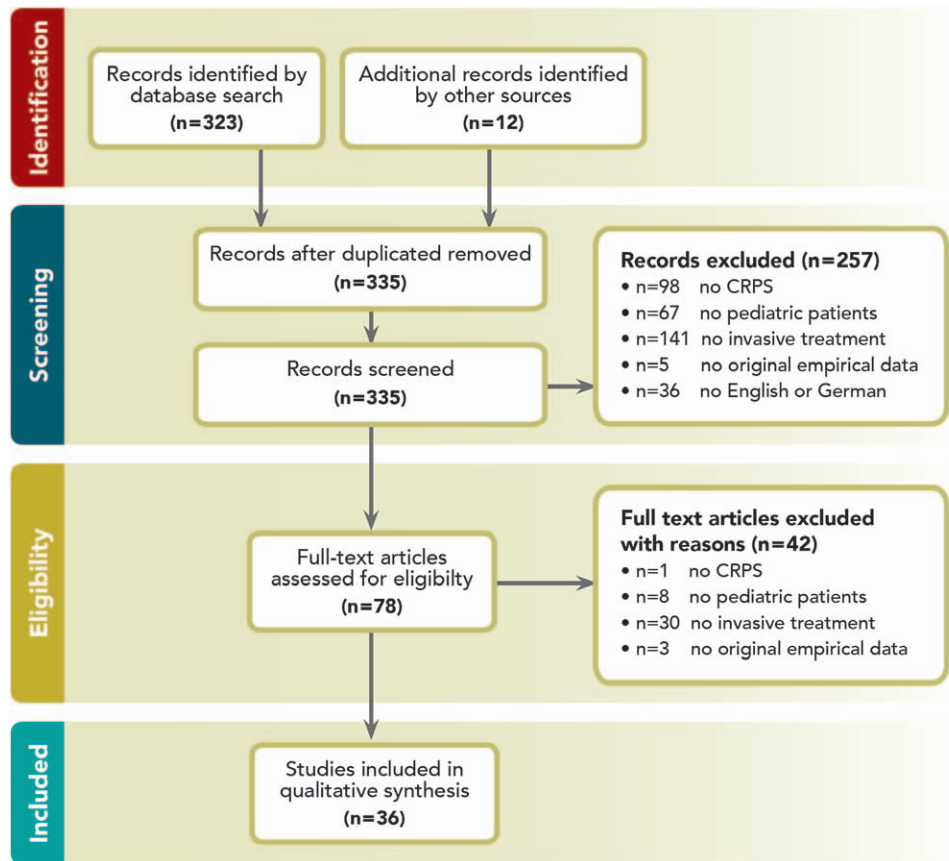


Fig. 1. Flowchart. CRPS = complex regional pain syndrome.

Table 1. Description of Patient and CRPS Characteristics

	Weighted mean n (%)
Age (n = 110)	13.2
Sex (n = 117)	
Female	97 (83%)
Male	20 (17%)
Affected limb (n = 88)	
Lower	72 (82%)
Upper	12 (14%)
Lower + upper	4 (4%)
Affected side (n = 56)	
Right	31 (55%)
Left	20 (36%)
Right + left	5 (9%)
Physical trauma (n = 75)	
No trauma	11 (15%)
Minor	52 (69%)
Major	12 (16%)

Total number of patients (N) of all studies = 173.

CRPS = complex regional pain syndrome.

Physiotherapy was not described in detail in most publications; only three works described different elements of the physiotherapeutic approach (e.g., mobilization, massage). In addition, 13 publications (36%) reported on psychotherapy and 24 (67%) on other conservative treatment. Other

conservative treatments mainly included pharmacotherapy but also transcutaneous electrical nerve stimulation and biofeedback. Pharmacotherapy predominantly consisted of nonsteroidal antiinflammatory drugs and antidepressants (table 3).

### Invasive Procedures

The procedure applied most often was singular sympathetic blocks, closely followed by epidural catheters and continuous sympathetic blocks (table 4). Peripheral/plexus regional anesthesia, intravenous regional blocks, and sympathectomy were applied less often. Rarely, SCS and pain-directed operations were used. In particular, sympathetic blocks were often performed more than once in a single individual patient (table 4). Multiple invasive procedures were applied to 86 patients (50%). For example, Kachko *et al.*<sup>21</sup> performed 12 stellate ganglion blocks in one patient, whereas others applied multiple intravenous regional blocks.<sup>20,23,24</sup> An escalation in the level of invasiveness, for example, sympathectomy after a single sympathetic block, was observed in several studies.<sup>25–29</sup>

The number of patients and the kind of invasive procedures reported in the literature changed during the analyzed period. The highest number of patients with CRPS receiving invasive treatment is reported in the nineties (fig. 2). In the seventies and eighties, destructive procedures such as sympathectomies are reported quite often. In the nineties, continuous sympathetic

**Table 2.** Quality Criteria of the Studies

	n (Total N)	Percentage
Objective clearly stated	33 (36)	92
Patient characteristics clearly described	35 (36)	97
Intervention clearly described	29 (36)	81
Outcome measures clearly defined	9 (36)	25
Outcomes measured before and after intervention	16 (36)	44
Statistical tests appropriate	4 (13)	31
Length of follow-up reported	18 (36)	50
Adverse events reported	12 (36)	33
Competing interests and source of support for the study reported	4 (36)	11

Depicts the number of studies fulfilling the stated criteria.

blocks were mainly described. Beginning with the new century, peripheral/plexus regional anesthesia and epidural catheters facilitating physiotherapy are reported more often.

### Conservative Treatment after Invasive Procedure

Information on conservative treatment applied after the invasive procedure was reported in 22 publications (61%). Specifically, 22 publications (61%) reported on physiotherapy, 12 (33%) on psychotherapy, and 19 (53%) on other conservative treatment. In studies reporting the specific conservative treatment, physiotherapy was applied in 100% of the patients. Most publications (n = 16) only reported about “physical therapy” or “physiotherapy” without any details on the specific elements. Some publications (n = 6) described the physiotherapy in more detail (*e.g.*, range of motion exercises, gait therapy, exercise against resistance, and assisted movement). In addition, psychotherapy was applied in 61% and other conservative treatments in 8% of the patients. A total of six patients (3%) received further analgesic treatment, and 11 patients (6%) received coanalgesics.

### Outcomes

Spontaneous pain outcomes were reported by most of the studies (86%), and allodynia and functional disability were

**Table 3.** Analgesics and Coanalgesics before Invasive Procedure

Medication	No. Patients Assessable,* n	No. Patients Receiving This Drug, n (%)
Opioids	79	11 (14)
Nonsteroidal antiinflammatory drugs	116	51 (44)
Other nonopioids	79	5 (6)
Anticonvulsants	86	22 (26)
Antidepressants	124	65 (52)
Other adjuvants†	86	22 (26)

\* For the different substances, between n = 5 and n = 10 studies it was not reported prior medication usage for the study patients. † Other adjuvants were calcitonin, clonazepam, steroids, tranquilizers, prostaglandin E1, and prazosin.

reported by 64 and 75% of the studies, respectively (table 5). Other CRPS-specific outcomes such as thermal pain and edema were rarely reported. According to the reported outcomes, approximately all patients who received invasive therapies showed an improvement in pain, other CRPS-related symptoms, and functional disability (table 5). In 32% of the pain outcomes and 8% of other outcomes, results were based on validated tools.

Side effects were seldom, and fatal consequences of the invasive procedure were never reported. Infections only occurred in two patients. Sixteen of 86 reported cases (19%) experienced a relapse.

### Discussion

A total of 36 studies including 173 pediatric patients who received invasive pain therapy for CRPS were reported. The methodological quality of the publications was generally low because most of them are case reports or case series representing level IV evidence. Only a minority of studies used the established diagnostic criteria for CRPS such as the ones proposed by the International Association for the Study of Pain.<sup>1</sup> Treatment before the invasive pain therapy was described in the majority of studies; the main focus was on physiotherapy. Most often, various sympathetic blocks, epidural catheters, and peripheral/plexus regional anesthesia were used as invasive procedures to treat pediatric CRPS. Positive outcomes after different invasive therapies were reported for most of the patients. A validated outcome tool, such as the visual analog scale, or a disability measure, such as the functional disability index,<sup>52</sup> was seldom used. Approximately half of the patients received multiple invasive interventions; additionally, many patients also underwent simultaneous conservative treatment. The follow-up for outcome assessment was rather short or not reported.

### Patients

The mean age of children who received an invasive pain therapy for CRPS was 13.2 yr, which is comparable with other CRPS pediatric populations that did not receive invasive therapies.<sup>10,11,13,15,53,54</sup> Comparable to patient characteristics in this review, approximately 80 to 90% of the children and adolescents diagnosed with CRPS in other studies were female.<sup>10,11,13,15,53,54</sup> Pediatric CRPS may show some differences compared to CRPS in adults. First, lower extremities are affected more often in pediatric CRPS (in 60 to 80% of the cases); second, a history of a severe physical trauma or operation is less often recalled in this group; third, children present less often with typical signs, such as edema, increase in temperature of the affected extremity, neurological symptoms such as tremor and paresis, or atrophies of skin, nails, and subcutaneous tissue.<sup>10,11</sup> Regardless of these frequently observed differences between children and adults, it seems that children who received invasive therapies present with signs and symptoms that are even more atypical for the condition called CRPS. For example, in the first case described



**Table 4.** Invasive Interventions for Complex Regional Pain Syndrome

Intervention	N (%)	No. Interventions per Patient; Weighted Mean (Range of Average)	Studies
Singular sympathetic blocks	56 (32%)	2 (1–12)	18,21,23,25–41
Epidural catheters	42 (24%)	1 (1–2)	18,21,25,26,29,30,32,40,42–45
Continuous sympathetic blocks	41 (24%)	1 (1–1.5)	22,23,25,29
Peripheral/plexus regional anesthesia	30 (17%)	1 (1–4)	16,21,34,39,40,45–49
Intravenous sympathetic and/or lidocaine blocks	30 (17%)	2 (1–6)	16,19,20,23–25,27,35,50
(Chemical) sympathectomy*	20 (12%)	1 (1–3)	17,22,25,27,28,36,41,47
Spinal cord stimulation	8 (5%)	1 (1–2)	26,30
Operations for pain treatment	3 (2%)	1	36,47,51
Intraspinal opioids or local anesthetics	2 (1%)	1	26,42
Other invasive treatment	2 (1%)	—	26,30

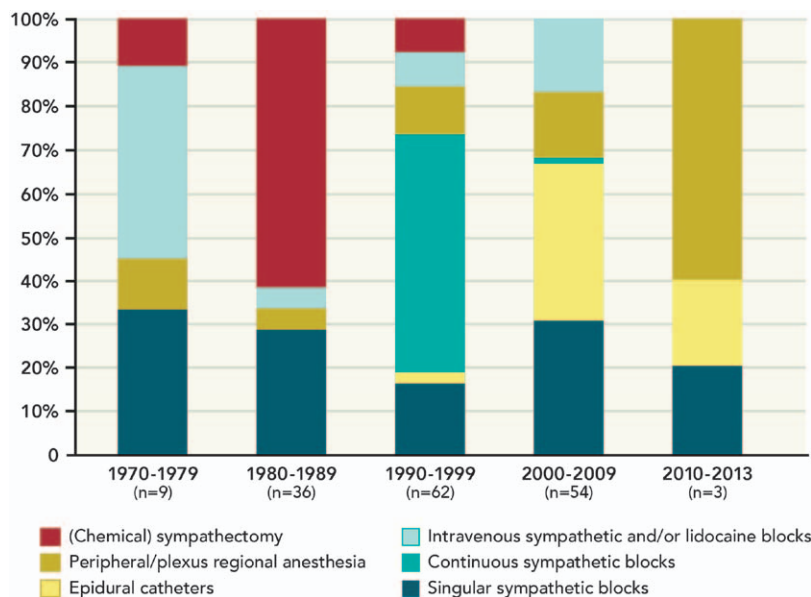
Total number of patients (N) of all studies = 173.

\* Detailed information on the procedure is only given in two articles; they use phenol<sup>27</sup> and ethyl alcohol to perform sympathectomy.<sup>25</sup> The remaining articles just reported a “sympathectomy,”<sup>17,22,36,41,47</sup> a “neurodestructive sympathectomy,”<sup>22</sup> or “thoroscopic sympathectomy.”<sup>28</sup>

by Dangel,<sup>25</sup> the right upper and lower extremity as well as the thorax and neck were affected. In the case reported by Martin *et al.*,<sup>46</sup> the right elbow and the left foot were involved. Olsson *et al.*<sup>30</sup> described a child experiencing five relapses after invasive SCS. Agarwal and Joseph<sup>31</sup> described a boy, who experienced CRPS in the right upper limb and 3 weeks later in the right leg and ankle. They considered this shift in symptoms to be a “recurrent migratory sympathetically maintained pain.” Tong and Nelson<sup>32</sup> reported a similar case in a child, who presented with CRPS of both arms (three times) and the right leg (one time) within a period of 5 yr and described the condition as “migratory reflex sympathetic dystrophy.” Others also described this progressive course of CRPS affecting different parts of the body.<sup>42</sup>

One hypothesis is that atypical cases of CRPS are more often unresponsive to standard treatment compared with

typical cases of CRPS and therefore invasive procedures are more often performed in atypical cases. Another hypothesis involves a publication bias for extremely atypical cases. A third potential explanation for the high number of atypical CRPS cases in this review might be that those children did not experience CRPS. The lack of the use of formal diagnostic criteria favors this explanation. Furthermore, psychological comorbidities are quite often reported by the authors. In the case series by Olsson *et al.*,<sup>30</sup> three of the seven children receiving SCS experienced a severe psychological disorder (sexual abuse with suicide attempt, anorexia nervosa, obsessive-compulsive disorder, and conversion disorders). Schiller<sup>33</sup> reported that five of the seven patients had a “psychological history”; four patients received invasive treatment and three of those four patients had psychological problems or severe psychiatric disorders (school phobia,



**Fig. 2.** Invasive complex regional pain syndrome treatment by decades. In this figure, only the six most frequent invasive treatments are displayed.

**Table 5.** Study Outcomes

Outcome Domain	No. Studies Reporting Outcome; N = 36 (100%)	No. Patients	Outcome		
			Improvement	No Change	Deterioration
Pain, spontaneous	31 (86%)	101	84 (83%)	16 (16%)	1 (1%)
Pain, allodynia	23 (64%)	54	48 (89%)	4 (7%)	2 (4%)
Pain, thermal pain	2 (6%)	3	3 (100%)	—	—
Thermal differences*	6 (17%)	8	8 (100%)	—	—
Edema	10 (28%)	10	10 (100%)	—	—
Functional disability	27 (75%)	81	80 (99%)	—	1 (1%)

\* Compared to contralateral extremity.

personality disorder, and paranoia); in a 15 yr old diagnosed with personality disorder, both legs were amputated during follow-up<sup>33</sup>. A girl reported by Martin *et al.*<sup>46</sup> refused to eat during treatment, and Kachko *et al.*<sup>21</sup> reported family and/or socioeconomic problems in 6 of 14 patients. Stanton *et al.*<sup>34</sup> reported that 83% of the 23 children undergoing psychological evaluation revealed some type of significant emotional dysfunction (“evidence of stressful situations, such as physical and sexual abuse or divorce of the parents, was often documented”).

According to the most recent diagnostic criteria of CRPS,<sup>2</sup> a “diagnosis that better explains the signs and symptoms” shall be ruled out. Importantly, this also includes psychiatric disorders. In adults, it has been described that symptoms very similar to CRPS arise due to psychiatric disorders.<sup>55</sup> We recommend the consultation of a child psychiatrist or child psychologist in case a CRPS is suspected in children and adolescents to rule out a psychiatric condition based on validated diagnostic measures.

### Invasive Pain Therapies

Invasive therapies for CRPS in children and adolescents are common. A major pain clinic performed invasive therapy in 35% of the pediatric patients with CRPS (*e.g.*, continuous lumbar sympathetic blocks and/or peridural catheters).<sup>56</sup> In the case series by Kachko *et al.*,<sup>21</sup> 29% received invasive treatment, and in the case series by Kesler *et al.*,<sup>57</sup> 33% received invasive treatment. In these studies, the first step is to attempt conventional approaches, and if those fail, invasive treatment options are applied.<sup>18,56</sup> However, the relevance of invasive therapies in children who do not respond to conventional treatments or medications is not proven in pediatrics,<sup>30,35</sup> and a positive publication bias for this stepwise approach must be assumed. Case reports with a bad outcome or those reporting therapy complications are rare.<sup>29,43,47</sup> Rand<sup>44</sup> described a patient who received inpatient therapy with an indwelling epidural catheter after conservative therapy had failed. After an initial improvement, the girl regressed substantially and became wheelchair bound but recovered to full function with the help of regular scheduled psychotherapy and physiotherapy.<sup>44</sup>

Similar experiences—effective conservative therapy after failure of an invasive approach—have been reported by Zernikow *et al.*<sup>54</sup> in a larger sample.

Sometimes, invasive therapies are extremely escalated and are reported without critical reflection on patient benefits and costs. For example, Dangel<sup>25</sup> described a case of left and right lower-extremity CRPS who was treated for 3 yr with four intravenous phentolamine tests, nine intravenous sympathetic blocks, and an unknown number of single and three continuous sympathetic blocks. Finally, five different chemical sympathectomies were performed resulting in neuralgia of the genitofemoral nerve. A significant improvement in CRPS symptoms was not reported. Olsson *et al.*<sup>30</sup> concluded that invasive SCS was positive in all of their pediatric patients with CRPS; for two patients, a partial remission was reported, and for five patients, a complete remission was reported. Due to our judgment of the case reports, this conclusion is highly questionable. One child improved despite, but not because of, the SCS; it was reported that this child did not respond to the stimulation even at high voltages, but the CRPS symptoms resolved during the subsequent 6 weeks. One child developed an infection, and the stimulator had to be extracted; before a second system could be implanted, a spontaneous remission occurred. The most aggressive form of invasive therapy has been reported for a 13-yr-old girl with three relapses of CRPS of the right lower extremity.<sup>26</sup> No prior conservative therapy or psychological counseling was reported. Invasive therapy consisted of at least three lumbar sympathetic blocks, a tunneled epidural catheter, two SCS implantations, and an intrathecal catheter (bupivacaine, sufentanil, and later application of ziconotide). No length of follow-up was reported, but the therapy was considered “effective” by the authors.<sup>26</sup> Wilder<sup>58</sup> summarized their experiences with SCS in children: “I know of least a half-dozen children who have undergone SCS for CRPS. The results have been mixed, ranging from modest improvement in pain and function to a worsening of pain, with explantation of the system (...).” Concerning his success of sympathectomy in childhood, he notes: “The three patients undergoing these procedures did not have improvement in pain scores despite improvement in circulation and edema (...).” (58p. 446).

### Effectiveness of Invasive Treatment

A final conclusion on the effectiveness of invasive therapies in the treatment of CRPS in children and adolescents cannot be drawn for several reasons. First, to date, only one placebo-controlled cross-over trial has been performed to test the effectiveness of invasive therapies and, specifically, the influence of lumbar sympathetic blocks on spontaneous and evoked pain and sensory thresholds and not on overall outcome.<sup>18</sup> The invasive procedure was part of a multidisciplinary approach.<sup>18</sup> All other studies have a lower level of evidence and methodological flaws. They do not allow a conclusion on a causal relation between procedure and outcome. Second, differences between children and adults have been insufficiently investigated. Those differences may play an important role in the diagnostic accuracy in classifying the symptoms of pediatric CRPS. Differential diagnoses, such as somatization disorders or other psychiatric disorders that cause CRPS-like symptoms due to nonuse of the extremity, need to be ruled out systematically based on standardized psychological diagnostic procedures. Without a reliable diagnosis of pediatric CRPS, conclusions on treatment effectiveness cannot be drawn. Third, a prominent problem in case studies is that the response to invasive treatment is often seen as a confirmation of the CRPS diagnosis. For example, Agarwal and Joseph<sup>31</sup> note that “In this case, the diagnosis was confirmed by the dramatic response to sympathetic blockade,” and Lloyd-Thomas and Lauder<sup>23</sup> reported “a percutaneous lumbar sympathetic block performed to aid diagnosis relieved the pain . . . .” The conclusion following such an approach is a confirmation of the diagnoses when the outcome is positive or a refusal of the diagnosis when the outcome is negative. Following this approach, bad outcomes will never be interpreted as inappropriate treatment. If conclusions on appropriate treatment are based on this approach, findings regarding the effectiveness of the therapy are strongly biased. Positive response to a sympathetic block is neither part of the established nor of the new proposed International Association for the Study of Pain criteria set to define CRPS.<sup>1,2</sup> Finally, many of the reported cases did not receive a single treatment. Either several invasive procedures were applied or additional conservative interventions were used.

### Interpretation of the Effectiveness

Several types of bias have to be considered when evaluating the role of invasive treatment in pediatric CRPS. The most important sources of misinterpretation are regression to the mean, spontaneous remission, placebo effect, observer bias, and publication bias toward positive outcomes. Furthermore, the quality of conservative, multimodal therapy seems to be extremely important for the outcome in pediatric CRPS. Zernikow *et al.*<sup>54</sup> showed that multimodal conservative intensive inpatient treatment results in favorable outcomes for most patients regardless of whether they previously received conservative and/or invasive therapies. Quality indicators for multimodal conservative treatment options in pediatric CRPS need to be developed. Such criteria could include (1)

structural quality criteria such as treatment intensity, specifics of different modules (*e.g.*, education, physiotherapy, occupational therapy, desensitization exercise, individual psychotherapy, family therapy, and school activities), staff characteristics (experience and multidisciplinary), and implementation of a home program after discharge<sup>11,56,59</sup> or (2) outcome quality criteria measured with a standardized approach. Before failure of conservative treatment is taken as a reason to consider invasive procedures as the last option, only high-quality conservative treatment should be implemented. Therefore, knowledge regarding such treatment needs to be extended. Reimbursement by health insurances needs to be adequate not only for invasive procedures but also for multidisciplinary rehabilitation and psychological treatment.

### Conclusions

The effectiveness of invasive therapies in the treatment of CRPS in children and adolescents is uncertain. The decision regarding the type of invasive procedure that should be applied when high-quality multimodal conservative treatment fails cannot yet be based on empirical data. Further case-controlled or randomized controlled studies with long-term follow-up periods and standardized outcome measures are urgently needed.

### Acknowledgments

Support was provided solely from institutional and/or departmental sources.

### Competing Interests

The authors declare no competing interests.

### Correspondence

Address correspondence to Dr. Zernikow: German Paediatric Pain Centre, Children's and Adolescents' Hospital, Dr.-Friedrich-Steiner Street 5, 45711 Datteln, Germany. b.zernikow@kinderklinik-datteln.de. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

### References

1. Merskey H, Bogduk N: Classification of Chronic Pain: Description of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd edition. Seattle, IASP Press, 1994
2. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR: Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med* 2007; 8:326–31
3. Veldman PH, Reynen HM, Arntz IE, Goris RJ: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 1993; 342:1012–6
4. Perez RS, Collins S, Marinus J, Zuurmond WW, de Lange JJ: Diagnostic criteria for CRPS I: Differences between patient profiles using three different diagnostic sets. *Eur J Pain* 2007; 11:895–902
5. Cepeda MS, Carr DB, Lau J: Local anesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database Syst Rev* 2005:CD004598

6. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R: Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev* 2004;CD003783
7. Straube S, Derry S, Moore RA, McQuay HJ: Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane Database Syst Rev* 2010;CD002918
8. Güler-Uysal F, Başaran S, Geertzen JH, Göncü K: A 2 ½-year-old girl with reflex sympathetic dystrophy syndrome (CRPS type I): Case report. *Clin Rehabil* 2003; 17:224–7
9. Goldschneider KR: Complex regional pain syndrome in children: Asking the right questions. *Pain Res Manag* 2012; 17:386–90
10. Tan EC, Zijlstra B, Essink ML, Goris RJ, Severijnen RS: Complex regional pain syndrome type I in children. *Acta Paediatr* 2008; 97:875–9
11. Logan DE, Carpino EA, Chiang G, Condon M, Firn E, Gaughan VJ, Hogan M, Leslie DS, Olson K, Sager S, Sethna N, Simons LE, Zurakowski D, Berde CB: A day-hospital approach to treatment of pediatric complex regional pain syndrome: Initial functional outcomes. *Clin J Pain* 2012; 28:766–74
12. Sherry DD, Wallace CA, Kelley C, Kidder M, Sapp L: Short- and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. *Clin J Pain* 1999; 15:218–23
13. Tan EC, van de Sandt-Renkema N, Krabbe PF, Aronson DC, Severijnen RS: Quality of life in adults with childhood-onset of Complex Regional Pain Syndrome type I. *Injury* 2009; 40:901–4
14. Sherry DD, Weisman R: Psychologic aspects of childhood reflex neurovascular dystrophy. *Pediatrics* 1988; 81:572–8
15. Logan DE, Williams SE, Carullo VP, Claar RL, Bruehl S, Berde CB: Children and adolescents with complex regional pain syndrome: More psychologically distressed than other children in pain? *Pain Res Manag* 2013; 18:87–93
16. Dadure C, Motais F, Ricard C, Raux O, Troncin R, Capdevila X: Continuous peripheral nerve blocks at home for treatment of recurrent complex regional pain syndrome I in children. *ANESTHESIOLOGY* 2005; 102:387–91
17. Greipp ME, Thomas AF, Renkun C: Children and young adults with reflex sympathetic dystrophy syndrome. *Clin J Pain* 1988; 4:217–21
18. Meier PM, Zurakowski D, Berde CB, Sethna NF: Lumbar sympathetic blockade in children with complex regional pain syndromes: A double blind placebo-controlled crossover trial. *ANESTHESIOLOGY* 2009; 111:372–80
19. Hannington-Kiff JG: Relief of Sudeck's atrophy by regional intravenous guanethidine. *Lancet* 1977; 1:1132–3
20. di Vadi PP, Brill S, Jack T, Brown C, Edwards T: Intravenous regional blocks with guanethidine and prilocaine combined with physiotherapy: Two children with complex regional pain syndrome, type I. *Eur J Anaesthesiol* 2002; 19:384–6
21. Kachko L, Efrat R, Ben Ami S, Mukamel M, Katz J: Complex regional pain syndromes in children and adolescents. *Pediatr Int* 2008; 50:523–7
22. Wilder RT, Berde CB, Wolohan M, Vieyra MA, Masek BJ, Micheli LJ: Reflex sympathetic dystrophy in children. Clinical characteristics and follow-up of seventy patients. *J Bone Joint Surg Am* 1992; 74:910–9
23. Lloyd-Thomas AR, Lauder G: Lesson of the week. Reflex sympathetic dystrophy in children. *BMJ* 1995; 310:1648–9
24. Papadopoulos GS, Xenakis TA, Arnautoglou E, Tefa L, Kitsoulis PB: The treatment of Reflex Sympathetic Dystrophy in a 9 year-old boy with long standing symptoms. *Minerva Anesthesiol* 2001; 67:659–63
25. Dangel T: Chronic pain management in children. Part II: Reflex sympathetic dystrophy. *Paediatr Anaesth* 1998; 8:105–12
26. Stanton-Hicks M, Kapural L: An effective treatment of severe complex regional pain syndrome type 1 in a child using high doses of intrathecal ziconotide. *J Pain Symptom Manage* 2006; 32:509–11
27. Doolan LA, Brown TC: Reflex sympathetic dystrophy in a child. *Anaesth Intensive Care* 1984; 12:70–2
28. Honjyo K, Hamasaki Y, Kita M, Harano K, Totoki T, Miyazaki S: An 11-year-old girl with reflex sympathetic dystrophy successfully treated by thoracoscopic sympathectomy. *Acta Paediatr* 1997; 86:903–5
29. Maneksha FR, Mirza H, Poppers PJ: Complex regional pain syndrome (CRPS) with resistance to local anesthetic block: A case report. *J Clin Anesth* 2000; 12:67–71
30. Olsson GL, Meyerson BA, Linderöth B: Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I). *Eur J Pain* 2008; 12:53–9
31. Agarwal V, Joseph B: Recurrent migratory sympathetically maintained pain syndrome in a child: A case report. *J Pediatr Orthop B* 2006; 15:73–4
32. Tong HC, Nelson VS: Recurrent and migratory reflex sympathetic dystrophy in children. *Pediatr Rehabil* 2000; 4:87–9
33. Schiller JE: Reflex sympathetic dystrophy of the foot and ankle in children and adolescents. *J Am Podiatr Med Assoc* 1989; 79:545–51
34. Stanton RP, Malcolm JR, Wesdock KA, Singen BH: Reflex sympathetic dystrophy in children: An orthopedic perspective. *Orthopedics* 1993; 16:773–9; discussion 779–80
35. Nordmann GR, Lauder GR, Grier DJ: Computed tomography guided lumbar sympathetic block for complex regional pain syndrome in a child: A case report and review. *Eur J Pain* 2006; 10:409–12
36. Ashwal S, Tomasi L, Neumann M, Schneider S: Reflex sympathetic dystrophy syndrome in children. *Pediatr Neurol* 1988; 4:38–42
37. Carron H, McCue F: Reflex sympathetic dystrophy in a ten year old. *South Med J* 1972; 65:631–2
38. Dietz FR, Mathews KD, Montgomery WJ: Reflex sympathetic dystrophy in children. *Clin Orthop Relat Res* 1990; 258:225–31
39. Franklin A, Austin T: The use of a continuous brachial plexus catheter to facilitate inpatient rehabilitation in a pediatric patient with refractory upper extremity complex regional pain syndrome. *Pain Pract* 2013; 13:109–13
40. Matsui M, Ito M, Tomoda A, Miike T: Complex regional pain syndrome in childhood: Report of three cases. *Brain Dev* 2000; 22:445–8
41. Wettrell G, Hallböök T, Hultquist C: Reflex sympathetic dystrophy in two young females. *Acta Paediatr Scand* 1979; 68:923–4
42. Farid IS, Heiner EJ: Intrathecal local anesthetic infusion as a treatment for complex regional pain syndrome in a child. *Anesth Analg* 2007; 104:1078–80
43. Ingelmo PM, Marino G, Fumagalli R: Sepsis after epidural catheterization in a child with chronic regional pain syndrome type I. *Paediatr Anaesth* 2005; 15:623–4
44. Rand SE: Complex regional pain syndrome in the adolescent athlete. *Curr Sports Med Rep* 2009; 8:285–7
45. Kato J, Gokan D, Ueda K, Shimizu M, Suzuki T, Ogawa S: Successful pain management of primary and independent spread sites in a child with CRPS type I using regional nerve blocks. *Pain Med* 2011; 12:174
46. Martin DP, Bhalla T, Rehman S, Tobias JD: Successive multisite peripheral nerve catheters for treatment of complex regional pain syndrome type I. *Pediatrics* 2013; 131:e323–6
47. Buchta RM: Reflex sympathetic dystrophy in a 14-year-old female. *J Adolesc Health Care* 1983; 4:121–2
48. Carayannopoulos AG, Cravero JP, Stinson MT, Sites BD: Use of regional blockade to facilitate inpatient rehabilitation of recalcitrant complex regional pain syndrome. *PM R* 2009; 1:194–8



49. Fermaglich DR: Reflex sympathetic dystrophy in children. *Pediatrics* 1977; 60:881–3
50. Suresh S, Wheeler M, Patel A: Case series: IV regional anesthesia with ketorolac and lidocaine: Is it effective for the management of complex regional pain syndrome 1 in children and adolescents? *Anesth Analg* 2003; 96:694–5
51. Parano E, Pavone V, Greco F, Majorana M, Trifiletti RR: Reflex sympathetic dystrophy associated with deep peroneal nerve entrapment. *Brain Dev* 1998; 20:80–2
52. Walker LS, Greene JW: The functional disability inventory: Measuring a neglected dimension of child health status. *J Pediatr Psychol* 1991; 16:39–58
53. Stanton-Hicks M: Plasticity of complex regional pain syndrome (CRPS) in children. *Pain Med* 2010; 11:1216–23
54. Zernikow B, Dobe M, Hirschfeld G, Blankenburg M, Reuther M, Maier C: [Please don't hurt me!: A plea against invasive procedures in children and adolescents with complex regional pain syndrome (CRPS)]. *Schmerz* 2012; 26:389–95
55. Mailis-Gagnon A, Nicholson K, Blumberger D, Zurowski M: Characteristics and period prevalence of self-induced disorder in patients referred to a pain clinic with the diagnosis of complex regional pain syndrome. *Clin J Pain* 2008; 24:176–85
56. Lee BH, Scharff L, Sethna NF, McCarthy CF, Scott-Sutherland J, Shea AM, Sullivan P, Meier P, Zurakowski D, Masek BJ, Berde CB: Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. *J Pediatr* 2002; 141:135–40
57. Kesler RW, Saulsbury FT, Miller LT, Rowlingson JC: Reflex sympathetic dystrophy in children: Treatment with transcutaneous electric nerve stimulation. *Pediatrics* 1988; 82:728–32
58. Wilder RT: Management of pediatric patients with complex regional pain syndrome. *Clin J Pain* 2006; 22:443–8
59. Brooke V, Janssewitz S: Outcomes of children with complex regional pain syndrome after intensive inpatient rehabilitation. *PM R* 2012; 4:349–54