

Intervertebral disc therapies for non-specific chronic low back pain: a systematic review and meta-analysis

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Abstract

Objectives: We aim to evaluate the benefits and harms of intervertebral disc therapies (IDTs) in people with non-specific chronic low back pain (NScLBP).

Methods: We conducted a systematic review and meta-analysis of randomized trials of IDTs versus placebo interventions, active comparators or usual care. EMBASE, MEDLINE, CENTRAL and CINHAL databases and conference abstracts were searched from inception to June 2020. Two independent investigators extracted data. The primary outcome was LBP intensity at short term (1 week–3 months), intermediate term (3–6 months) and long term (after 6 months).

Results: Of 18 eligible trials (among 1396 citations), five assessed glucocorticoids (GCs) IDTs and were included in a quantitative synthesis; 13 assessed other products including etanercept ($n=2$), tocilizumab ($n=1$), methylene blue ($n=2$), ozone ($n=2$), chymopapaine ($n=1$), glycerol ($n=1$), stem cells ($n=1$), platelet-rich plasma ($n=1$) and recombinant human growth and differentiation factor-5 ($n=2$), and were included in a narrative synthesis. Standardized mean differences (95% CI) for GC IDTs for LBP intensity and activity limitations were -1.33 [-2.34 ; -0.32] and -0.76 [-1.85 ; 0.34] at short term, -2.22 [-5.34 ; 0.90] and -1.60 [-3.51 ; 0.32] at intermediate term and -1.11 [-2.91 ; 0.70] and -0.63 [-1.68 ; 0.42] at long term, respectively. Odds ratios (95% CI) for serious and minor adverse events with GC IDTs were 1.09 [0.25; 4.65] and 0.97 [0.49; 1.91].

Conclusion: GC IDTs are associated with a reduction in LBP intensity at short term in people with NScLBP. Positive effects are not sustained. IDTs have no effect on activity limitations. Our conclusions are limited by high heterogeneity and a limited methodological quality across studies.

Registration PROSPERO: CRD42019106336.

Keywords: intervertebral disc, intradiscal therapy, low back pain, systematic review

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Introduction

Low back pain (LBP) is a symptom defined as pain between the last ribs and the gluteal area. It is the primary cause of years lived with disability worldwide during the past three decades for both sexes combined.¹ If LBP duration exceeds 12 weeks, it is considered chronic LBP (cLBP).² When no underlying condition (i.e. infection, tumor or inflammation) is found, cLBP is considered non-specific (NScLBP).^{3,4} NScLBP

can be related to various plausible anatomical nociceptive sources, including the intervertebral disc (ID).^{5,6}

An increasing number of trials assessed the benefits and harms of ID therapies (IDTs) in people with NScLBP supposedly originating from the ID. IDT could be defined as an injection of a drug or a medical device directly into the ID, under fluoroscopic guidance. The effects of IDTs

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are assumed to rely on three mechanisms: (1) because of limited blood flow, delivering a drug directly into the ID could be more efficient than systemic treatments;⁷ (2) during ID degeneration, pro-inflammatory soluble mediators are locally released,⁸ so intradiscal injection of a drug targeting inflammation could combat biochemical adverse factors;⁹ and (3) during ID degeneration, changes in biomechanical properties of the ID occur, so intradiscal injection of devices could combat biomechanical adverse factors.⁷

The effects of IDTs depend on the nature of the drug or device injected. Four main mechanisms of action have been described: (1) a reduction of local inflammation with IDT of glucocorticoids (GCs),¹⁰ anti-tumor necrosis factor- α (TNF- α),¹¹ anti-interleukin-6 (IL-6),¹² and methylene blue);^{13–15} (2) a removal of ID herniation with IDT of collagenase,¹⁶ chymopapaine¹⁷ or ethanol gel);¹⁸ (3) a stimulation of ID healing with IDT of platelet-rich plasma (PRP)¹⁹ or stem cells;¹⁶ and (4) a restoration of the ID biomechanical properties with IDT of an intradiscal device¹⁶ or ozone.²⁰

Despite growing experimental and clinical data, the benefits and harms of IDTs for people with NScLBP remain debated. We aimed to review evidence on the benefits and harms of IDTs in people with NScLBP.

Materials and methods

Our study was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019106336). We made no changes to the protocol or outcomes. All outcomes prespecified in the protocol are reported in the manuscript. This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Appendix 1).²¹

Data sources

We searched for articles in EMBASE, MEDLINE, CENTRAL and CINHAL databases from inception to 13 July 2018. Our search was updated on 11 June 2020. The search strategy combined controlled vocabulary and free word text based on the synonyms of “intradiscal” and “low back pain” (Appendices 2 and 3). We limited our search to studies of humans and adults, without language restrictions. Study included were randomized controlled trial (RCT) and quasi-RCT

defined as trial with a prospective identification of participants but using inadequate randomization approaches. Other meta-analyses and systematic reviews, cohort studies, case reports, case series, cross-sectional studies and studies assessing effectiveness on radicular pain as the primary outcome were excluded. We also hand-searched the references lists of selected trials identified from electronic searches and proceedings of physical and rehabilitation medicine, rheumatology and radiology from French and international conferences, and ClinicalTrials.gov.

Study selection and outcomes

The two first authors (board-certified rheumatologists) independently reviewed titles and abstracts, then full-text articles to assess eligibility. We included RCTs of adults (range 18 years and older) with NScLBP who received IDT *versus* a comparator. In the absence of a consensual definition of IDT, we defined IDT as an injection of a drug, biological product, gas or device using a needle inserted into the ID. We defined the comparator as (1) placebo (i.e. sham procedure or insertion of a needle into the ID with or without intradiscal injection of contrast, saline, anesthetic or supposedly inactive agent), (2) active intradiscal comparator (i.e. intradiscal injection of the same product but at a different dosage or intradiscal injection of a different supposedly active agent), (3) other non-intradiscal spinal injection therapies (i.e. epidural, intradural, foraminal or facet joint injections of GCs), or (4) usual care (i.e. unstandardized non-pharmacological and/or pharmacological treatment prescribed at the discretion of the treating physician). We did not consider as an IDT or a comparator radiofrequency denervation, intradiscal electrothermal or laser therapies, lumbar surgery or any other lumbar procedures requiring general anesthesia, because no drug or medical device was injected into the ID during these interventions. Efficacy outcomes were patient-centered relevant core outcomes:²² LBP intensity and LBP-specific activity limitations. Safety outcomes were immediate and post-IDT minor and serious adverse events as classified by the WHO-UMC system.²³

Data extraction

The two first authors independently extracted data on study characteristics, design, population, interventions, outcomes and funding sources by using a standardized extraction form (Appendix

4). Corresponding authors were contacted to collect missing data. For individual studies, the psycho-social risk factors of the population were assessed with available demographic and socio-professional information by two independent investigators, who were blinded to the other characteristics of the study. Psycho-social risk was defined as the risk of persistent activity limitations or work participation restriction at 12 months after the intervention according to the expert. Psycho-social risk factors were rated as low, moderate, high or unclear. The quality of the studies was assessed with JADAD scale, which evaluates randomization process, blinding, withdrawals and dropouts. The total score ranges from 0 (low-quality study) to 5 (high-quality study). A JADAD score ≥ 4 was considered good quality.²⁴ Discrepancies were resolved by a consensus process between the two investigators and a third investigator in case of unresolved discrepancies. As requested by peer reviewers, we added assessments of the overall risk of bias *a posteriori*, using the Cochrane Risk of Bias tool.²⁵ Because there is low correlation between assessments of risk of bias using the Cochrane Risk of Bias tool and assessments of quality using the JADAD scale, we decided to keep the JADAD scoring also.²⁶ Studies of low quality were not excluded because we wanted to comprehensively report all currently available evidence addressing the research question. Rather than excluding studies of low quality, we decided to rate the quality of evidence as high, moderate, low, and very low, indicating a gradient of confidence in estimates of treatment effect,²⁷ so that the readers can fully interpret the results presented.

Data synthesis

We conducted meta-analyses using a random-effect model with an inverse variance method for studies showing sufficient homogeneity in terms of design and comparator by using RevMan 5.3. Statistical heterogeneity was measured with the Cochran chi-square test and I^2 statistic.²⁸ Outcomes were analyzed at three timepoints: (1) short term (1 week–<3 months), intermediate term (3– \leq 6 months) and long term (>6 months) by using the most consistently reported duration data within each category. For continuous outcomes, scores were converted to means (standard deviations¹⁹), as recommended by the Cochrane collaboration,²⁵ and pooled as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Effects were considered null with

SMD <0.2, weak with SMD 0.2–0.5, moderate with SMD 0.5–0.8 and large with SMD >0.8.²⁹ For dichotomous outcomes, we expressed the results for individual trials as odds ratios (ORs). For multiple arm studies, we combined relevant experimental groups and relevant comparator groups to avoid arbitrary omission or double counting of participants. Studies of low quality were included in the systematic review and meta-analysis. Only additional sensitivity analyses excluded poor-quality (JADAD score <3) and outlier studies. Publication bias was not assessed because the number of eligible trials was inadequate to draft a funnel plot. The strength of each body of evidence was summarized as high, moderate, low or very low according to the quality, consistency and precision of aggregated studies.^{27,30} When a quantitative synthesis was not appropriate because of high heterogeneity or a too small number of studies, we provided a narrative synthesis.

Results

Studies

Our search yielded 1396 relevant references: 1347 were excluded on the basis of titles and abstracts and 23 after full-text review. Among the 26 remaining articles, eight had no available data and were excluded (Figure 1). Eighteen trials were included. Two trials included more than 100 participants, with sample sizes ranging from 15 to 135 participants.^{31,32} Ten trials assessed IDTs targeting local inflammation: five GCs,^{31–35} two anti-TNF- α ,^{36,37} one anti-IL-6¹² and two methylene blue.^{13,15} Four trials assessed IDTs aiming at promoting disc healing: two recombinant human growth and differentiation factor-(rhGDF-5),^{38,39} one PRP⁴⁰ and one stem cells.⁴¹ Two trials assessed IDTs targeting disc protrusion: one chymopapain⁴² and one glycerol.⁴³ Two trials assessed IDTs aimed at restoring disc height by using ozone.^{44,45} Comparators were placebo in 16/18 (88.88%) trials: one comparator was a sham procedure with intramuscular injection of anesthetic⁴¹ and 15 comparators were intradiscal injections of anesthetic,^{12,15,34,36,43} saline,^{13,31,33,35,37} contrast alone,^{32,40} excipients^{38,39} or distilled water.⁴² Comparators were an active intradiscal comparator in 1/18 (5.55%) trials (ozone at a different dosages)⁴⁴ and usual care in 1/18 (5.55%).⁴⁵ No trial used another type of spinal injection as a comparator. Characteristics of the studies are in Table 1. Only 6/18 (33.33%)

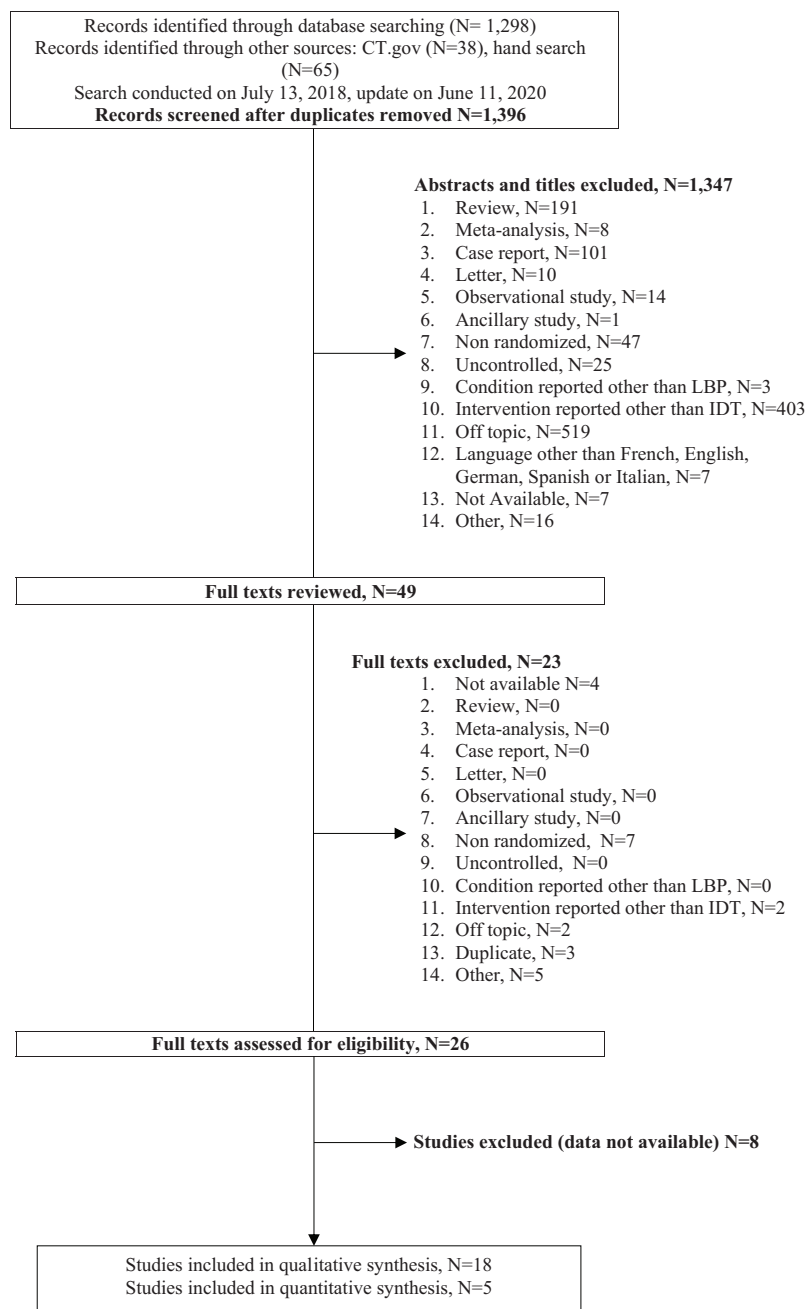


Figure 1. Flow diagram.

studies had a JADAD score ≥ 4 .^{13,15,31,32,34,40} Concerns were raised regarding the randomization and blinding methods, and 6/18 (33.33%) studies did not provide sufficient information regarding withdrawals and dropouts (Appendices 5, 6). All the 18 studies were considered for analyses, regardless of their overall quality. As requested by peer reviewers, the overall risk of bias was also summarized *a posteriori* using the Cochrane Risk of Bias tool (Appendix 7).

Participants

Participants' mean (SD) age was 45.2 (6.4) years, disease duration 4.2 (2.9) years and LBP intensity 63.8/100 (16.9); 2/18 (11.11%) studies exclusively included patients with Modic one changes.^{32,34} Information regarding psycho-social risk factors of participants was provided in 9/18 (50.0%) reports: risk factors were considered low in one study,⁴⁴ moderate in five studies^{15,31,33,36,42} and high in three studies.^{32,34,37}

Effectiveness

Glucocorticoids. Five trials ($n=436$ participants)^{31–35} compared GC IDTs ($n=235$) with placebo [i.e. intradiscal saline ($n=114$),^{31,33,35} intradiscal contrast alone ($n=63$)³² and intradiscal anesthetic ($n=24$)³⁴] at short, intermediate and long term. The studies showed reduced LBP intensity favoring GC IDTs at short term [SMD (95% CI): -1.33 ($-2.34; -0.32$), $I^2=89\%$, moderate strength of evidence (MOE)] but not intermediate term [SMD (95% CI): -2.22 ($-5.34; 0.90$), $I^2=99\%$, low strength of evidence (LOE)] or long term [SMD (95% CI): -1.11 ($-2.91; 0.70$), $I^2=98\%$, MOE] (Figure 2). We found no significant reduction in LBP-specific activity limitations at short term [SMD (95% CI): -0.76 ($-1.85; 0.34$), $I^2=92\%$, LOE], intermediate term [SMD (95% CI): -1.60 ($-3.51; 0.32$), $I^2=97\%$, LOE] or long term [SMD (95% CI): -0.63 ($-1.68; 0.42$), $I^2=96\%$, MOE] (Figure 3). On sensitivity analysis, we confirmed no reduction in LBP intensity at intermediate term [SMD (95% CI): -0.74 ($-2.72; 1.25$), $I^2=96\%$] and long term [SMD (95% CI): 0.17 ($-0.54; 0.88$), $I^2=77\%$] and found no reduction in LBP-specific activity limitations at intermediate term [SMD (95% CI): -0.74 ($-2.05; 0.57$), $I^2=89\%$] and long term [SMD (95% CI): 0.03 ($-0.23; 0.29$), $I^2=0\%$] (Table 2; Appendices 8a and 8b).

Etanercept. Two trials ($n=96$)^{36,37} compared etanercept IDT ($n=60$) with placebo [i.e. intradiscal saline ($n=6$) and intradiscal anesthetic ($n=30$)] at short term. The SMD (95% CI) was 0.03 ($-1.08; 1.15$; $I^2=79\%$, LOE) for LBP intensity and 0.26 ($-0.78; 1.30$; $I^2=76\%$, LOE) for LBP-specific activity limitations (Table 3, appendices 9a and 9b).

Tocilizumab. One trial ($n=60$)¹² compared tocilizumab IDT ($n=30$) with placebo [i.e. intradiscal saline ($n=30$)] at short term. The SMD (95% CI) was -0.71 ($-1.23; -0.18$) for LBP intensity and -0.97 ($-1.50; -0.43$) for

Table 1. Study characteristics.

Title	Author (Country)	Year	Jadad score	Modic 1 only	Participants age (years)*	LBP duration (years)†	Psychosocial risk	LBP intensity (/100)‡	IDTG size	IDT	CG size	Comparator	Outcomes	Timepoints
Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes	Cao <i>et al.</i> ³¹ (China)	2011	4	No	42.3	NR	B	68	80	3 ml diprosan or 1 ml diprosan + 2 ml songmeite	40	3 ml intradiscal saline	VAS ODI	3 months 6 months
Implication of two different doses of intradiscal ozone-oxygen injection upon the pain alleviation in patients with low back pain: A randomized, single-blind study	Elawamy <i>et al.</i> ³⁴ (Egypt)	2018	3	NR	40.2	NR	A	82	30	10 ml (40 µg/ml) ozone	30	10 ml (30 µg/ml) intradiscal ozone	VAS ODI	1 month 6 months
The use of intradiscal steroid therapy for lumbar spinal discogenic pain: a randomized controlled trial	Khot <i>et al.</i> ³³ (UK)	2004	2	NR	42.8	NR	B	32	46	1 ml (40 mg) methylprednisolone acetate	52	1 ml intradiscal saline	VAS ODI	12 months
Intradiscal glycerol or bupivacaine in treating low back pain	Kotilainen <i>et al.</i> ⁴³ (Finland)	1997	1	NR	47.0	8.0	Unclear	58	9	1 ml 50% glycerol	6	2 ml intradiscal 0.5% bupivacaine	VAS ODI	0.5 month
Intradiscal glucocorticoid injection for patients with chronic low back pain associated with active discopathy: a randomized trial	Nguyen <i>et al.</i> ³² (France)	2017	5	Yes	46.0	6.3	C	69	67	1 ml (25 mg) prednisolone acetate + 1 ml contrast	68	1 ml intradiscal contrast	NRS QBPDs	1 month 3 months 6 months
Therapeutic effect of medical ozone on lumbar disc herniation	Niu <i>et al.</i> ⁴⁵ (China)	2018	1	NR	48.0	NR	Unclear	87	60	Ozone - 20 µg/ml - 40 µg/ml - 60 µg/ml	20	Usual care	VAS	6 months
Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial	Noriega <i>et al.</i> ⁴¹ (Spain)	2017	3	NR	38.0	NR	Unclear	65	12	25 × 10 ⁶ allogeneic MSCs in 2 ml saline	12	2 ml intramuscular 1% mepivacaine	VAS ODI	1 week 3 months 6 months
A randomized placebo-controlled trial of intradiscal methylene blue injection for treating chronic discogenic low back pain	Peng <i>et al.</i> ¹⁵ (China)	2010	4	NR	41.7	3.4	B	70	36	1 ml (10 mg) methylene blue + 1 ml 2% lidocaine	36	1 ml intradiscal 2% lidocaine	NRS ODI	6 months

Continued

Table 1. (Continued)

Title	Author (Country)	Year	Jadad score	Modic 1 only	Participants age (years)*	LBP duration (years)†	Psychosocial risk	LBP Intensity (/100)†	IDTG size	IDT	CG size	Comparator	Outcomes	Timepoints
Single intradiscal administration of the tumor necrosis factor- α inhibitor, etanercept, for patients with discogenic low back pain	Sainoh <i>et al.</i> ³⁶ (Japan)	2016	2	NR	61.3	NR	B	82	38	10 mg etanercept + 2 ml 0.5% bupivacaine	39	2 ml intradiscal 0.5% bupivacaine	NRS ODI	1 month
Single intradiscal injection of the interleukin-6 receptor antibody tocilizumab provides short-term relief of discogenic low back pain; prospective comparative cohort study	Sainoh <i>et al.</i> ¹² (Japan)	2015	2	NR	60.2	NR	Unclear	84	30	40 mg tocilizumab + 1–2 ml 0.5% bupivacaine	30	2 ml intradiscal 0.5% bupivacaine	NRS ODI	1 month
Lumbar intradiscal platelet-rich plasma (prp) injections: a prospective, double-blind, randomized controlled study	Tuakli-Wosornu <i>et al.</i> ⁴⁰ (USA)	2016	5	NR	42.6	NR	Unclear	47	29	1–2 ml PRP	18	1–2 ml intradiscal contrast	NRS	1 month
A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy	Cohen <i>et al.</i> ³⁷ (USA)	2007	3	NR	39.3	5.3	C	43	30	Etanercept - 0.1 mg - 0.25 mg - 0.5 mg - 0.75 mg - 1.0 mg - 1.5 mg	6	0.5 ml intradiscal saline	VAS ODI	1 month
Étude en double aveugle du traitement de la lombosciatique discale par chimionucléolyse	Feldman <i>et al.</i> ⁴² (France)	1986	3	No	42.5	1.1	B	35	20	2 ml (400 UI) chymopapain	19	2 ml intradiscal distilled water	VAS	1 month 3 months
Diagnosis of discogenic low back pain in patients with probable symptoms but negative discography	Yu <i>et al.</i> ³⁵ (China)	2012	3	NR	44.9	2.1	Unclear	68	23	5 mg dexamethasone + contrast	22	Intradiscal saline + contrast	VAS ODI	1 month 3 months 6 months
A clinical trial to evaluate the safety, tolerability and preliminary effectiveness of single administration intradiscal rhgdf-5 for the treatment of early stage lumbar disc degeneration	DePuy ³⁸ (Korea)	2014	3	NR	42.1	NR	Unclear	NR	22	1 mg rhGDF-5	9	Intradiscal excipients: trehalose, glycine and hydrogen chloride	VAS ODI	12 months

(Continued)

Table 1. (Continued)

Title	Author (Country)	Year	Jadad score	Modic 1 only	Participants age (years)*	LBP duration (years)†	Psychosocial risk	LBP Intensity (/100)†	IDTG size	IDT	CG size	Comparator	Outcomes	Timepoints
A multicenter, randomized, double-blind, placebo controlled, clinical trial to evaluate the safety, tolerability and preliminary effectiveness of 2 doses of intradiscal rhGDF-5 (single administration) for the treatment of early stage lumbar disc degeneration	DePuy ²⁹ (USA)	2014	3	NR	42.2	NR	Unclear	NR	14	rhGDF-5 - 1 mg - 2 mg	10	Intradiscal excipients: trehalose, glycine and hydrogen chloride	VAS ODI	12 months
Intradiscal glucocorticoids injection in chronic low back pain with active discopathy: a randomized controlled study	Tavares <i>et al.</i> ³⁴ (France)	2017	4	Yes	50.0	1.9	C	64	24	2 ml (50 mg) prednisolone acetate	26	2 ml intradiscal 2% lidocaine	VAS ODI	1 month 3 months 6 months
A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain : the IMBI study	Kallewaard <i>et al.</i> ¹³ (Netherlands)	2019	5	No	41.9	9.4	Unclear	66	40	1 ml (10 mg) methylene blue + 0.5 ml 2% lidocaine + 0.5 ml contrast	41	1 ml intradiscal saline + 0.5 ml 2% lidocaine + 0.5 ml contrast	NRS ODI	6 weeks 3 months 6 months

*Baseline values.

Psychosocial risk: A, weak; B, moderate; C, high.

CG, comparator group; IDTG, intradiscal therapy group; LBP, low back pain; MSCs, mesenchymal stem cells; NR, not reported; NRS, numeric rating scale; ODI, Oswestry disability index ; PRP, platelet-rich plasma; QBPDI, Quebec back pain disability index; VAS, visual analogue scale.

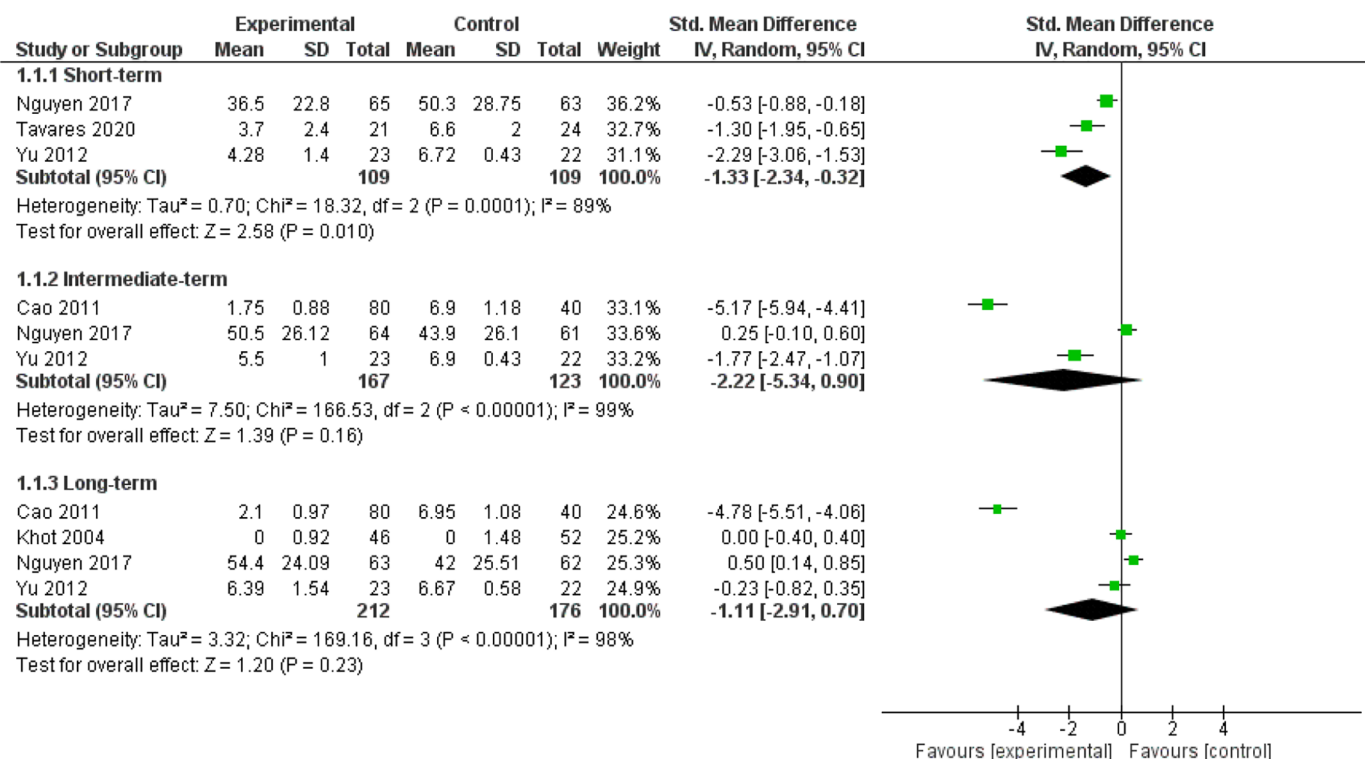


Figure 2. Forest plot for pain, comparing intervertebral disc therapies (IDTs) of corticosteroid versus placebo.

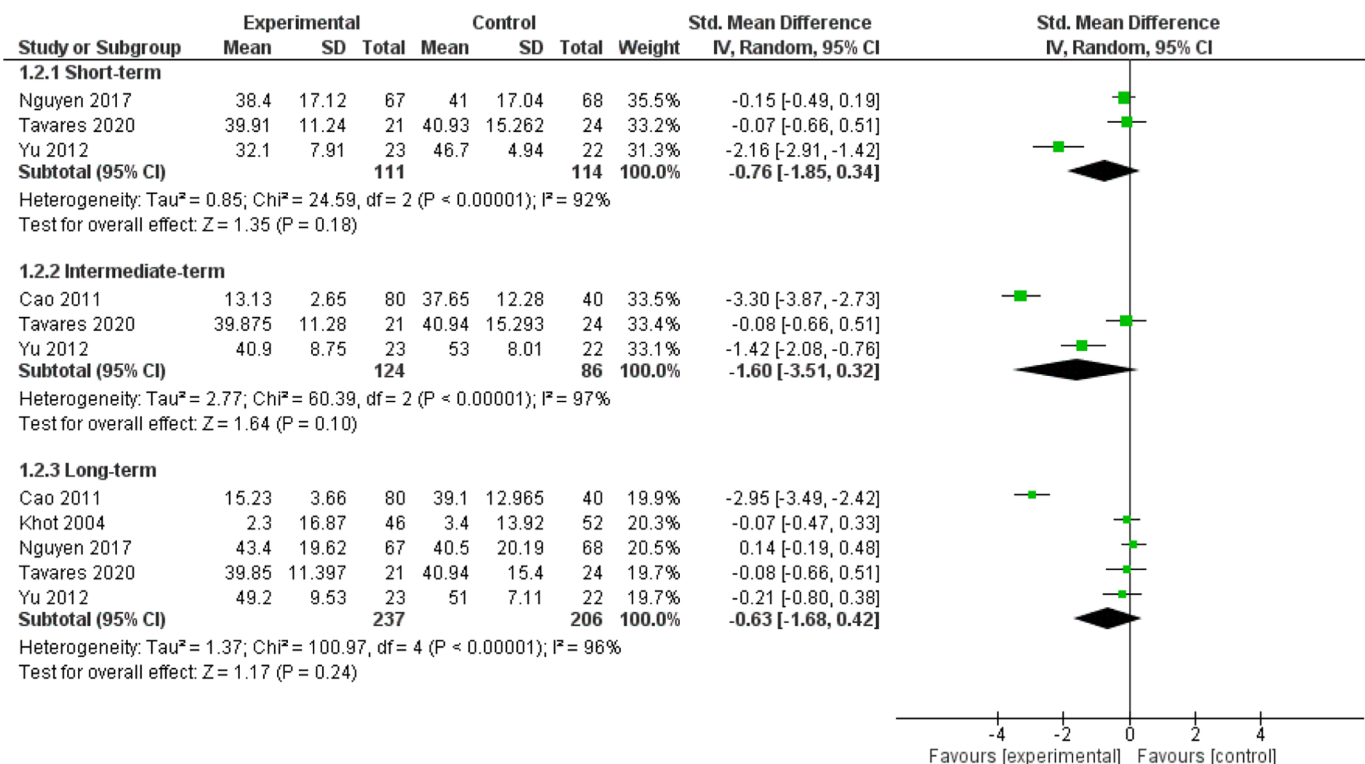


Figure 3. Forest plot for activity limitations, comparing intervertebral disc therapies (IDTs) of corticosteroids versus placebo.

Table 2. Effects on low back pain, activity limitations and adverse events of glucocorticoid intervertebral disc therapies *versus* placebo.

Authors	Glucocorticoid	Comparator	N	Pain intensity (SMD)	Activity limitations (SMD)	Major AE (OR)	Minor AE (OR)
Cao <i>et al.</i> ³¹	Diprospan 3 ml Diprospan 1 ml + Songmeile 2 ml	Saline IDT	120	Intermediate term: -5.17 [-5.94; -4.41] Long term: -4.78 [-5.51; -4.06]	Intermediate term: -3.30 [-3.83; -2.73] Long term: -2.65 [-3.49; -2.42]	NR	NR
Khot <i>et al.</i> ³³	Methylprednisolone acetate 40 mg in 1ml	Saline IDT	98	Long term: 0.00 [-0.40; 0.40]	Long term: -0.07 [-0.47; 0.33]	NR	NR
Nguyen <i>et al.</i> ³²	Prednisolone acetate 25 mg in 1 ml + 1 ml of contrast	Contrast IDT	135	Short term: -0.53 [-0.88; -0.18] Intermediate term: 0.25 [-0.10; 0.60] Long term: 0.50 [0.14; 0.85]	Short term: -0.15 [-0.49; 0.19] Long term: 0.14 [-0.19; 0.48]	3.09 [0.12; 77.21]	0.97 [0.49; 1.91]
Tavares <i>et al.</i> ³⁴	Prednisolone acetate 50 mg (2ml)	Lidocain IDT	50	Short term: -1.30 [-1.95; -0.65]	Short term: -0.0 [-0.66; 0.51] Intermediate term: -0.08 [-0.66; 0.51] Long term: -0.08 [-0.66; 0.51]	0.83 [0.16; 4.24]	0
Yu <i>et al.</i> ³⁵	Dexamethasone 5 mg + contrast	Saline + contrast IDT	45	Short term: -2.29 [-3.06; -1.53] Intermediate term: -1.77 [-2.47; -1.07] Long term: -0.23 [-0.82; 0.35]	Short term: -0.76 [-1.85; 0.34] Intermediate term: -1.42 [-2.08; -0.76] Long term: -0.21 [-0.80; 0.38]	NR	NR

AE, adverse events; IDT, intervertebral disc therapies; NR, not reported; OR, odds ratio; SMD, standardized mean differences.

Table 3. Effects on low back pain, activity limitations and adverse events of biological intervertebral disc therapies *versus* placebo.

Authors	Intervention	Comparator	N	Pain intensity (SMD) at short term	Activity limitations (SMD) at short term	Major AE (OR)	Minor AE (OR)
Cohen <i>et al.</i> ³⁷	Etanercept	Saline IDT	36	0.67 [-0.23; 1.56]	0.86 [-0.04; 1.77]	NR	NR
Sainoh <i>et al.</i> ³⁶	Etanercept	Bupivacaine IDT	77	-0.48 [-0.99; 0.04]	-0.21 [-0.72; 0.30]	0	0
Sainoh <i>et al.</i> ¹²	Tocilizumab	Bupivacaine IDT	60	-0.71 [-1.23; -0.18]	-0.97 [-1.50; -0.43]	3.10 [0.12; 79.23]	0

AE, adverse events; IDT, intervertebral disc therapies; NR, not reported; OR, odds ratio; SMD, standardized mean differences.

LBP-specific activity limitations, favoring tocilizumab IDT (Table 3, appendix 10a and 10b).

Methylene blue. Two trials ($n=152$)^{13,15} compared methylene blue IDT ($n=76$) with placebo [i.e. intradiscal anesthetic ($n=36$) or intradiscal anesthetic and isotonic saline ($n=41$)] at short, intermediate and long term. They revealed no statistically significant difference between the two

groups for LBP intensity at short term [SMD (95% CI): -0.18 (-0.62; 0.25)], intermediate term [SMD (95% CI): -0.12 (-0.56; 0.32)] or long term [SMD (95% CI): -1.32 (-3.75; 1.11)] or for LBP-specific activity limitations at short term [SMD (95% CI): -0.28 (-0.72; 0.16)], intermediate term [SMD (95% CI): -0.08 (-0.51; 0.36)] or long term [SMD (95% CI): -1.64 (-4.63; 1.35)] (Table 4, appendices 11a and 11b).

Table 4. Effects on low back pain, activity limitations and adverse events of other intervertebral disc therapies *versus* placebo.

Authors	Intervention	Comparator	N	Pain intensity (SMD)	Activity limitations (SMD)	Major AE (OR)	Minor AE (OR)
NCT01124006 ³⁹ ; NCT01182337 ³⁸	rhGDF5	Excipient IDT	55	Long term: -0.07 (-0.76; 0.62)	Long term: -0.01 (-0.58; 0.55)	1.48 [0.30; 7.35]	1.56 [0.37; 6.68]
Elawamy <i>et al.</i> ⁴⁴ ; Niu <i>et al.</i> ⁴⁵	Ozone	Ozone IDT (other dosage) Usual care	60 80	Short term: 0.20 (-0.51; 0.91) Long term: 0.30 (-2.21; 0.91) Long term: -0.62 (-2.43; 1.20)	Short term: 0.10 (-0.19; 0.39) Long term: -0.04 (-0.19; 0.11)	NR NR	NR NR
Kotilainen <i>et al.</i> ⁴³	Glycerol	Anesthetic IDT	11	Short term: -0.03 (-1.56; 1.50)	Short term: 0.19 (-1.34; 1.73)	NR	NR
Tuakli <i>et al.</i> ⁴⁰	PRP	Contrast IDT	47	Short term: -0.27 (-0.86; 0.32)	Short term: -0.05 (-0.64; 0.53)	NR	NR
Noriega <i>et al.</i> ⁴¹	Stems cells	IM anesthetic	72	Short term: 0.68 (-0.15; 1.51) Intermediate term: -0.10 (-0.90; 0.70) Long term: -0.37 (-1.37; 0.44)	Short term: 0.41 (-0.40; 1.22) Intermediate term: -0.49 (-1.31; 0.32) Long term: -0.44 (-1.25; 0.37)	0	0.17 [0.03; 0.98]
Peng <i>et al.</i> ¹⁵	Methylen blue	Anesthetic IDT	71	Long term: -2.57 (-3.51; 1.93)	Long term: -3.18 (-3.89; 2.47)	NR	NR
Kallewaard <i>et al.</i> ¹³	Methylen blue	Saline + lidocaine + contrast IDT	81	Short term: -0.18 (-0.62; 0.25) Intermediate term: -0.12 (-0.56; 0.32) Long term: -1.32 (-3.37; 1.11)	Short term: -0.28 (-0.72; 0.16) Intermediate term: -0.08 (-0.51; 0.36) Long term: -0.13 (-0.57; 0.32)	5.39 [0.25; 115.86]	NC
Feldman <i>et al.</i> ⁴²	Chymopapain	Distilled water IDT	38	Short term: \searrow 55% <i>versus</i> 26% Intermediate term: \searrow 65% <i>versus</i> 42%	short term: \searrow 36 % <i>versus</i> 19 %	0.43 [0.12; 1.59]	0.28 [0.01; 7.44]

AE, adverse events; IDT, intervertebral disc therapies; IM, intramuscular; NR, Not Reported; OR, odds ratio; SMD, standardized mean differences.

Ozone. Two trials ($n=140$)^{44,45} assessed the effectiveness of ozone IDT. Elawamy *et al.*⁴⁴ ($n=60$) compared two different doses of ozone IDT [40 $\mu\text{g/ml}$ ($n=30$) *versus* 30 $\mu\text{g/ml}$ ($n=30$)]. The trials showed no statistically significant difference between the two groups for LBP intensity at short term [SMD (95% CI): -0.14 (-0.64; 0.37)] or long term [SMD (95% CI): 0.30 (-2.21; 0.81)] or for LBP-specific activity limitations at short term [SMD (95% CI): 0.17 (-0.34; 0.68)] or long term [SMD (95% CI): -0.14 (-0.64; 0.37)] (Table 4, Appendices 12a and 12b). Niu *et al.*⁴⁵ ($n=80$ participants) compared ozone IDT ($n=60$) with usual care ($n=20$). The SMD (95% CI) was -1.32 (-1.87; -0.77) for LBP intensity at long term (Table 4, Appendix 13).

Chymopapaine. One trial ($n=39$)⁴² compared chymopapaine IDT ($n=20$) with placebo (i.e. intradiscal distilled water [$n=19$]). The authors reported a reduction in LBP intensity of 55% and 65% at short and intermediate term in the experimental group *versus* 26% and 42% in the comparator group and a reduction of LBP-specific activity limitations of 36% at short term in the experimental group *versus* 19% in the comparator group (Table 4).

Glycerol. One trial ($n=11$)⁴³ compared glycerol IDT ($n=9$) with placebo [i.e. intradiscal anesthetic ($n=2$)] at short term. The SMD (95% CI) was -0.03 (-1.56; 1.50) for LBP intensity and 0.19 (-1.34; 1.73) for LBP-specific activity limitations (Table 4, Appendices 14a and 14b).

Stem cells. One trial ($n=24$)⁴¹ compared stem-cell IDT ($n=12$) with placebo [i.e. intramuscular anesthetic ($n=12$)] at short, intermediate and long term. The SMDs (95% CI) were 0.68 (-0.15; 1.51), -0.10 (-0.90; 0.70) and -0.37 (-1.17; 0.44) for LBP intensity and 0.41 (-0.40; 1.22), -0.49 (-1.31; 0.32) and -0.44 (-1.25; 0.37), respectively, for LBP-specific activity limitations (Table 4, Appendices 15a and 15b).

Platelet-rich plasma. One trial ($n=47$)⁴⁰ compared PRP IDT ($n=29$) with placebo [i.e. intradiscal contrast alone ($n=18$)] at short term. The SMD (95% CI) was -0.27 (-0.86; 0.32) for LBP intensity and -0.05 (-0.64; 0.53) for LBP-specific activity limitations (Table 4, Appendices 16a and b).

RhGDF-5. Two trials ($n=55$ participants)^{38,39} compared rhGDF-5 IDT ($n=36$) with placebo [i.e. intradiscal excipients (trehalose, glycine and HCl) ($n=19$)] at long term. The SMD (95% CI) was -0.07 (-0.76; 0.62) $I^2=33\%$, LOE, for LBP intensity and -0.01 (-0.58; 0.55) $I^2=0\%$, LOE, for LBP-specific activity limitations (Table 4, Appendices 17a and b).

Harms

Overall, 9/17 (52.9%) studies (ozone, PRP, glycerol, methylene blue, 3/5 GC and 1/3 biologics studies) did not report safety outcomes. For GC IDT, two studies^{32,34} involving 180 participants reported 8/180 serious adverse events [OR 1.09 (95% CI 0.25; 4.65)] and 69/180 minor adverse events [0.97 (0.49; 1.91)] (Tables 2, 3, 4, Appendix 18). For biologics IDT, two studies^{12,36} involving 120 participants reported 1/120 serious adverse event [OR 3.10 (95% CI 0.12; 79.23)] and 0/120 minor adverse events. For chymopapain IDT,⁴² the authors reported 1/38 serious adverse event [OR 0.43 (95% CI 0.12; 1.59)] and 1/38 minor adverse events [0.28 (0.01; 4.44)]. For stem cells IDT,⁴¹ authors reported 1/24 minor adverse event [OR 0.17 (95% CI 0.03; 0.98)] and no serious adverse event. Finally, for rhGDF-5 IDT, two studies^{38,39} involving 55 participants reported 1/55 serious adverse event [OR 1.60 (95% CI 0.34; 7.57)] and 1/55 minor adverse event [1.48 (0.37; 5.98)].

Discussion

We found GC IDTs associated with reduced LBP intensity at short term in people with

NScLBP. Positive effects were not sustained. We found no effect on activity limitations. However, it is difficult to conclude that GC IDTs were significantly associated with reduced LBP intensity at short term based on a meta-analysis of three studies with only 218 participants. For other IDTs, evidence is limited because of the small number of studies.

After a local injection of GCs, systemic effects persist for 21 days but are not observed beyond then,⁴⁶ which may explain why the positive effects of GC IDTs are not sustained. We observed no effect of GC IDTs on LBP-specific activity limitations, despite some discrepancies (no effect in the Nguyen *et al.*³² and Tavares *et al.*³⁴ trials and important effects favoring GC IDTs in the Cao *et al.*³¹ and Yu *et al.*³⁵ trials), with consistent results on sensitivity analyses. However, activity limitations and participation restrictions are complex dimensions of human functioning and unlikely to improve after an IDT as a stand-alone intervention.

For biologics IDT, Sainoh *et al.*^{12,36} reported moderate positive effects of tocilizumab IDT at short term and a similar trend for etanercept IDT. Conversely, Cohen *et al.* did not find a positive effect of etanercept IDT at short term.³⁷ Some clinical and methodological differences may explain these results. The Cohen *et al.* study was a small multi-arm ($n=6$) trial, comparing different doses of etanercept, from 0.1 to 1.5 mg. Experimental data suggest that effective doses of etanercept range from 10 to 20 mg,⁴⁷ closer to those used in the Sainoh *et al.* study. Niu *et al.*⁴⁵ reported a large effect of ozone IDT [SMD -1.32 (95% CI -1.87; -0.77)] *versus* usual care at long term. However, these findings have not been replicated by independent groups and the overall risk of bias was high. Peng *et al.*¹⁵ reported large effects with methylene blue IDT at long term for both pain and activity limitation. The overall risk of bias was low, but the sample size was small.¹⁵ In addition, the evolution of pain in the comparator group was unusual.¹⁵ These results were not replicated in the Kallewaard *et al.*¹³ study. We included the effects of other IDTs in a narrative synthesis. Overall, we found no clear effects of these IDTs for both LBP intensity and activity limitation. No studies raised serious safety concerns, but adverse events were rarely reported.

Our review has limitations. First, we found heterogeneity across studies regarding interventions and

comparators. After grouping interventions according to the therapeutic intradiscal agent used, groups were small and a quantitative synthesis was possible only for GC IDTs *versus* placebo. As the number of studies suitable for meta-analyses is low, it could be of interest to perform some aspects of qualitative systematic review for the other studies to glean directions for future studies. Among studies assessing the same intradiscal agent, we found heterogeneity for doses and injected volumes. Most of the comparators were placebo interventions, but the nature of the agent injected, doses and volumes varied across studies. The rationale for using these placebo interventions was poor, and a specific negative effect cannot be ruled out. This situation may explain the unusual evolution reported in the comparator group of some studies such as symptom stagnancy or even worsening.^{34,35} We also found heterogeneity for populations. Participants had various levels of psycho-social risk factors. In addition, clinical and/or imaging findings consistent with a plausible anatomical nociceptive source (i.e. ID) were rarely reported. Second, the overall methodological quality of the included studies was limited. Concerns were raised regarding the randomization and blinding processes: among the five studies assessing GC IDTs, four had an unclear blinding process^{31,33-35} and two had an unclear randomization process.^{31,33} The statistical heterogeneity found in our meta-analysis could be a result of both clinical and methodological diversities. Finally, some IDTs were designed to target radicular pain rather than LBP, but we assessed only LBP. Furthermore, we purposely excluded radiofrequency denervation, electro-thermal and laser therapies because no drug or device was injected into the ID during these interventions. However, to our knowledge, there is no consensus about what an IDT is.

In summary, limited evidence suggests that GC IDTs are associated with a reduction in LBP intensity at short term in people with NScLBP. For other IDTs, we found no clear effects. Because positive effects of GC IDTs are not sustained, studies aiming at assessing the effect of intradiscal therapy using anti-inflammatory molecules with a longer lasting effect such as mesenchymal stem cells or PRP are currently ongoing (e.g. NCT03737461 and NCT03712527, respectively).

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Conception and design of the study. CD, AF, MMLC, FR, CN.

Drafting of the original protocol. CD, MMLC, FR, CN.

Acquisition of data. CD, SL, MB, FS, CN.

Coordination of the study. CN.

Design of the statistical analysis plan. CD, CN.

Data analysis and interpretation. CD, SL, CN.

Drafting of the present manuscript. CD, SL, CN.

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Conflict of interest statement

AF, MMLC, FR and CN are authors of the following article “Nguyen C, Boutron I, Baron G, Sanchez K, Palazzo C, Benchimol R, Paris G, James-Belin É, Lefèvre-Colau MM, Beaudreuil J, Laredo JD, Béra-Louville A, Cotten A, Drapé JL, Feydy A, Ravaut P, Rannou F, Poiraudou S. *Intradiscal Glucocorticoid Injection for Patients With Chronic Low Back Pain Associated With Active Discopathy: A Randomized Trial*. *Ann Intern Med*. 2017 Apr18; 166(8):547–556,” which reported the positive effect of an intradiscal injection of glucocorticoids on pain at short term in patients with chronic low back pain and active discopathy.

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Data availability statement to your paper

Data will be available upon request by contacting Associate Professor Christelle Nguyen (christelle.nguyen2@aphp.fr).

Supplemental material

Supplemental material for this article is available online.

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