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Review

Collagenase *Clostridium histolyticum* for Peyronie's disease: a contemporary atlas of complications and their management

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Abstract

Introduction: Collagenase *Clostridium histolyticum* (CCH) remains the only Food and Drug Administration–approved medical treatment for Peyronie's disease (PD). The initial IMPRESS I and II trials (Investigation for Maximal Peyronie's Reduction Efficacy and Safety), which led to Food and Drug Administration approval, revealed a rate of treatment-related adverse events as high as 84%. Studies fail to provide clear definitions of complications.
Objectives: To review complications, provide a CCH complication atlas, and propose management strategies for commonly encountered complications.
Methods: We performed a literature review using PubMed. A photographic atlas was provided regarding complications in patients in a high-volume CCH center for PD.
Results: Complications were identified and classified by nature and severity. We followed a standardized previously published grading system for hematomas. Complications include bruising, swelling, hematoma formation, back pain, and, rarely, corporal rupture. Complications were discussed, and hematomas were graded by penile surface area. Complication photographs were graded and displayed. Treatment-related adverse effects do not affect overall results.
Conclusion: Recognizing and grading complications associated with CCH therapy for PD is crucial for effective patient management and informed decision making. A standardized grading system allows for consistency in reporting and comparing hematoma complication rates across studies and patient populations. Herein we provide images that will help clinicians identify and confidently manage common complications that may occur in any CCH program.

Keywords: Peyronie's disease; collagenase Clostridium histolyticum; Xiaflex; penile injections; complications; atlas.

Introduction

Peyronie's disease (PD) is characterized by the formation of fibrous plaques within the tunica albuginea of the penis, resulting in penile angulation and associated deformities. PD is often associated with erectile pain and/or dysfunction.[1] The exact pathophysiology driving the development of PD is not entirely understood; however, PD plaques are characterized, in part, by increased deposition of disorganized type I and III collagen related to an inflammatory response.[2-4]

The IMPRESS I and II trials (Investigation for Maximal Peyronie's Reduction Efficacy and Safety) were published in 2013 and led to the Food and Drug Administration's approval of collagenase *Clostridium histolyticum* (CCH), which remains the only such approved medical treatment for PD. CCH is composed of 2 collagen-degrading enzymes, derived from the bacterium *C histolyticum*.[5] The standard injection technique proposed during the IMPRESS trials involves injecting CCH in a linear track inside the fibrous plaque, while withdrawing the needle. Typically, 2 injections and penile modeling are performed every 6 weeks for 4 cycles to complete a treatment round. Modified techniques have been described to improve efficacy or reduce adverse effects.[6]

CCH complications are often cited as a treatment-limiting concern for clinicians.[7] Complications include bruising, swelling, hematoma formation, back pain, and, rarely, corporal rupture.[8] Numerous studies have assessed the efficacy and safety of CCH therapy for PD, with promising results; however, complications described in these studies lack clear definitions.[6] For example, a recent study mentioned penile discoloration as an adverse effect but did not define it.[9] To mitigate ambiguity in describing these complications, Amighi et al proposed a penile hematoma classification, which can be useful in accurately identifying and managing a subset of complications.[6]

Standardizing complication-related terminology may help clinicians better evaluate their patients after CCH injection and to confidently address such adverse events. Here, we provide a CCH complication atlas and propose management strategies for commonly encountered complications.

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Methods

Literature review

We performed a literature review using PubMed with the following keywords: "Peyronie's disease," "Collagenase *clostridium histolyticum*," "Xiaflex," "complications," "injection," "adverse," "hematoma," "bruising," "treatment," "technique," and other terms related to our topic of interest. We included studies published in English that described complication rates, management, and complication definitions related to CCH therapy for PD.

Complication definitions

Complications were identified and classified by nature and severity. We followed a standardized grading system for hematomas, as previously published.

Hematoma formation was characterized by the simultaneous occurrence of bruising and swelling at the injection site, without any loss of erection. Instances where bruising and swelling occurred separately and not at the injection site were not categorized as hematomas. We defined swelling as edema without any associated bruising. Grades I, II, and III were categorized by how much of the penile surface area was affected by the hematoma, with specific approaches to clinical treatment for each grade. Grade I hematomas encompass less than one-third of the penile surface area; grade II, between one-third and one-half; and grade III, greater than one-half.[6]

In contrast to hematoma, a corporal rupture following CCH therapy was defined by the loss of erections in conjunction with extensive swelling and bruising at the injection site. A blood blister was defined as a superficial outpouching of blood within the epidermis, lacking underlying swelling or bruising.

Ethics

All images presented in this article were taken in a high-volume CCH injection treatment program. This report and the associated images are aligned with the guidelines established by the Health Insurance Portability and Accountability Act. All images were edited to omit any patient identifiers or protected health information. Institutional review board approval was not required at our institution, given the use of deidentified photographs for educational and scientific purposes.

Injection technique

The standard CCH injection technique involves puncturing the lesion and injecting the enzyme into the needle track while withdrawing it. In the attempt to improve efficacy and reduce risk of complications, modified techniques had been developed and described. The "fan" technique described by Amighi et al is reported to deliver a better safety profile as compared with the standard technique.[6] This was the technique of choice for the injections in this series. The technique consisted of injecting one-third of the total dosage into 3 distinct locations in the plaque in a fan or trident shape (Figure 1).

Results

The safety and efficacy of CCH were first evaluated by the multicenter IMPRESS trials, which were large double-blinded, placebo-controlled phase III trials that demonstrated the effectiveness of CCH in improving penile curvature. However, these studies also showed that >84% of participants who received CCH reported a treatment-related adverse event (TRAE). Most TRAEs were considered mild, such as ecchymosis (80%), penile swelling (55%), and pain (46%). Of note, the investigators of the IMPRESS trial included hematoma, contusion, bruising, and hemorrhage under the umbrella term "ecchymosis."[10] This issue followed in subsequent studies, perpetuating dubious definitions of complications with different clinical relevance.[11-17]

Penile pain and edema

Most complications related to CCH are mild and self-limiting. Penile pain and edema are expected adverse effects; incident rates range from 9.9% to 55.0% (Table 1).[10,18] Pain and edema do not impede treatment continuity and may be managed with elastic pressure dressings and ice packs, as well as by limiting strenuous activity.[8] Caution should be taken when applying pressure dressings, as glans ischemia, although rare, has been reported.[19] In our experience a dressing that is too proximal and tight may also result in distal edema (Figure 2A).

Back pain

Another complication that can be encountered is back pain. In a report by Sigalos et al, 5.8% patients in a cohort of >300 patients experienced acute lower back pain during an intralesional CCH treatment course (Table 1). This appeared to be more common in patients who underwent >1 round of CCH injections (6-8 injections) due to the presence of multiple plaques (8.7% and 6.9% during second and third rounds, respectively, vs 1.3% during first round). The pain typically occurred shortly after injection and was self-limiting or resolved following a single dose of nonsteroidal anti-inflammatory medication, including ibuprofen or intramuscular ketorolac (Toradol) for the most severe cases that occurred in the office setting.[20]

Hypersensitivity reactions

Rarely, a small group of patients may experience a hypersensitivity reaction, characterized by mild pruritis accompanied by rash. In a report of 1044 patients undergoing CCH, Carson et al reported such a reaction in 3 patients (0.003%) (Table 1). The mechanism by which this occurs is not fully understood, but it is likely a response to the bacterial-derived enzymes after immune system sensitization.[15] Although this is rare, clinicians should be aware of the possibility of allergy-like reactions when providing CCH treatment.

Ecchymoses and hematomas

Ecchymoses and hematomas are distinct clinical entities. Unfortunately, the IMPRESS trials did not distinguish these as unique adverse events but instead collated them into the same category.[10] The lack of specificity in distinguishing these 2 adverse events persisted in studies following the IMPRESS trials, further perpetuating the issue.[11-17]

Colloquially, ecchymosis can be described as bruising, which typically occurs when self-contained bleeding spreads within the subcutaneous tissue without collecting or filling space; the result is changes in skin color. Initially, there is a purple discoloration to the skin, and with time it turns to green, then yellow, as hemoglobin degrades into

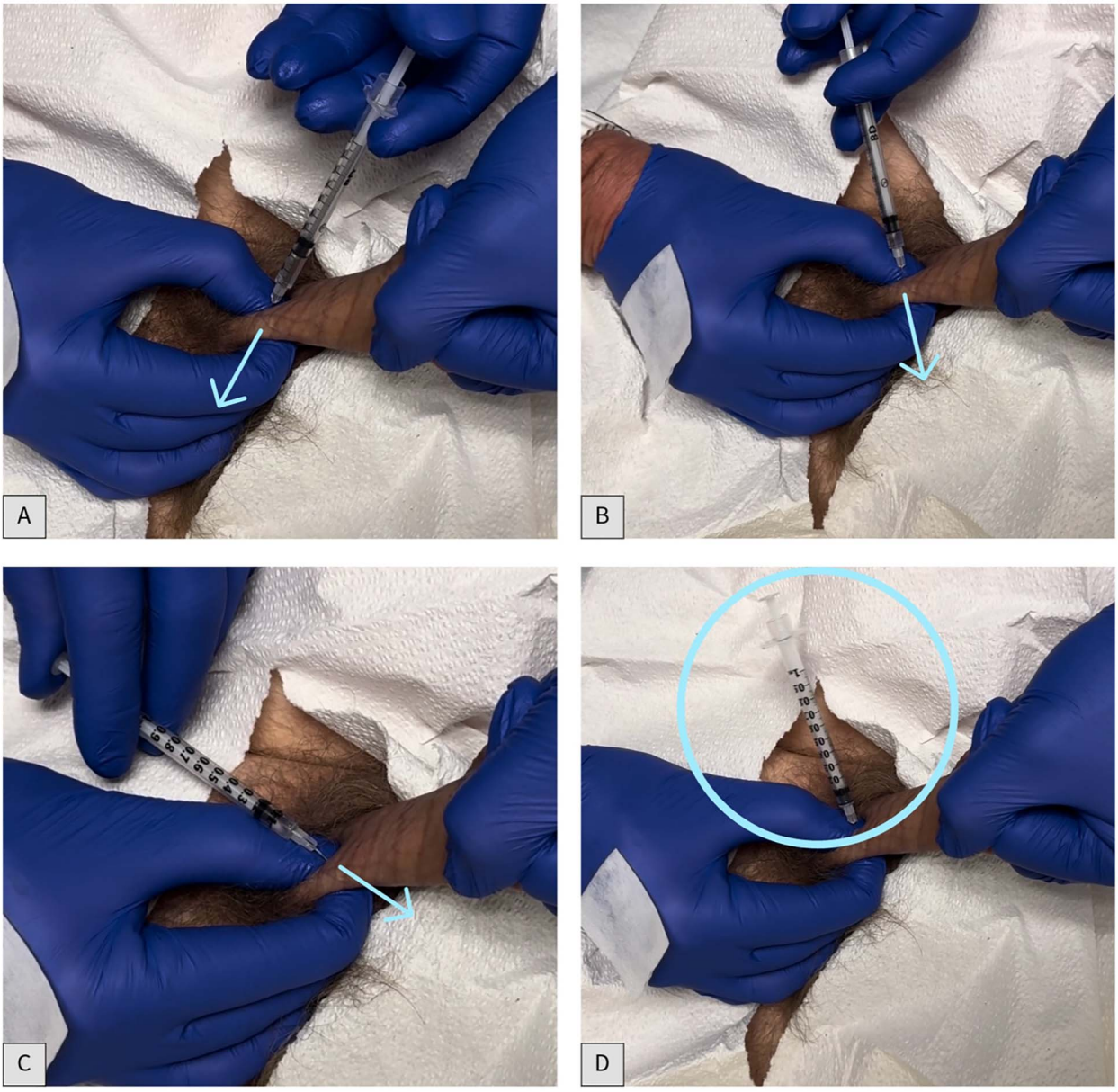

Figure 1. (A-C) "Fan" technique: needle positioning. (D) The needle should hold in place when positioned freely, like a dart, meaning correct positioning in the Peyronie's plaque.

Table 1. Complication incidence.

Complication	Incidence, %	High-yield reference
Penile pain and edema	9.9-55	Gelbard et al[10,18]
Back pain	5.8	Sigalos et al[20]
Hypersensitivity reactions	0.003	Carson et al[15]
Hematoma	5.3[a]-80	Amighi et al[6], Gelbard et al[10]
Corporal rupture	0.05-4.9	Gelbard et al,[10] Hughes et al[21]

[a] Equally distributed across grade and severity.

its subproducts. Ecchymoses are one of the most frequent adverse effects of CCH treatment for PD: present in nearly 55% of patients undergoing treatment.[6] The size of the discoloration can range from pinpoint at the injection location or large enough to cover the scrotum and subpubic region—often associated with localized swelling. The latter is usually referred to as diffuse ecchymosis or "mushroom" ecchymosis if it spreads to the suprapubic fat pad (Figure 2B and 2C). In our experience, this type of TRAE is mild and self-limiting; further intervention is not often required. However, sometimes a compressive wrap can be used when patients are symptomatic.

In contrast, a hematoma occurs when there is a collection of blood in a confined space. CCH is a destructive treatment that degrades collagen, a structural protein; therefore, it can also degrade the tunica albuginea tissue causing a microtear

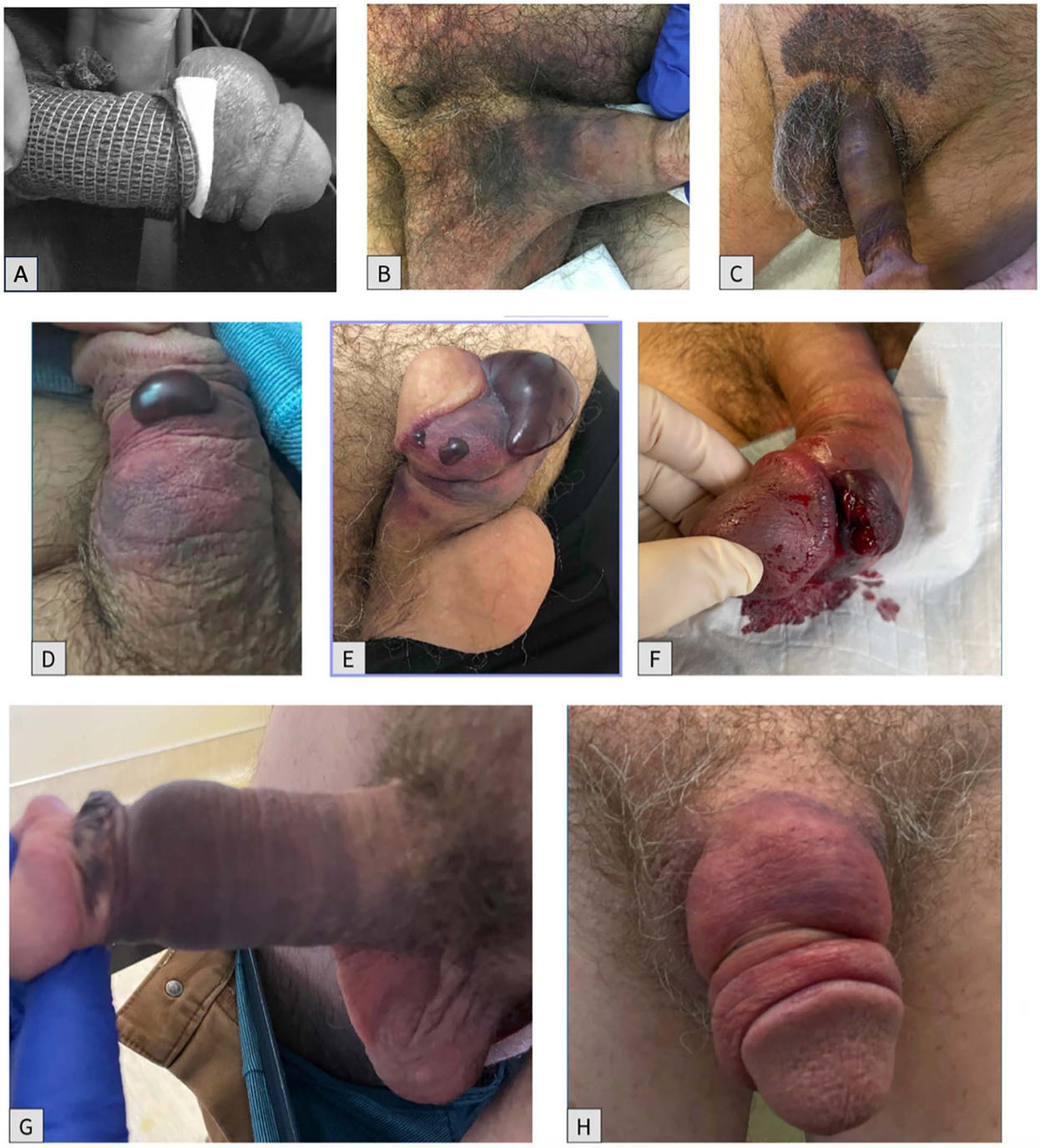

Figure 2. (A) Distal penile edema due to tight compression wrap. (B) Ecchymosis. (C) "Mushroom" ecchymosis. (D) Blood blister. (E) Grade I hematoma with associated blood blister. (F) Hematoma/blood blister drainage. (G) Grade II hematoma. (H) Grade III hematoma.

and extravasation of blood. Most of the time, these injuries are self-resolving. Amighi et al proposed a comprehensive hematoma classification system with clearly defined characteristics that help urologists accurately identify, describe, and manage complications.[6]

Hematomas are defined as a simultaneous occurrence of bruising and swelling at the injection site. Amighi et al found the hematoma incidence rate to be 5.3% (Table 1) and equally distributed across grade and severity.[6] A summary of hematoma definitions and management is provided in Table 2. Grade I hematomas are self-confined collections of blood affecting no more than one-third of the total penile length (Figure 2E); this grade should not delay treatment. Closely related to lower-grade hematomas, blood blisters are thin bullae filled with blood. In our practice, this localized and superficial epidermal outpouching of blood usually does not require any intervention other than reassurance and a compression wrap for 24 hours before reassessment (Figure 2D). However, aspiration and drainage should be considered when it is large enough to cause any pain or discomfort (Figure 1F).

Grade II hematoma measures between one-third and half the penile length (Figure 2G); 1 week for recovery before reinjecting is advisable. Grade III hematoma is defined as

Table 2. Hematoma definitions.[6]

Hematoma grade	Definition	Proposed management[a]
Ecchymosis	Bruising or discoloration of the skin.	None required
Blood blister	Superficial epidermal outpouching of blood without underlying swelling or bruising.	Often none required; drainage if discomfort or pain
Grade I	Concurrent swelling and bruising involving less than one-third of the surface area of the penis.	Often none required; should not delay treatment
Grade II	Concurrent swelling and bruising involving more than one-third and less than half of the surface area of the penis.	1-wk treatment delay[b]
Grade III	Concurrent swelling and bruising involving more than half of the surface area of the penis.	2-wk treatment delay[b]
Corporal rupture	Concurrent swelling and bruising and loss of erections.	Conservative approach; treatment should be delayed until total recovery

[a] Proposed management items do not affect treatment efficacy. [b] Or until plaque is palpable; may require drainage.

greater than half the penile length (Figure 2H); we advise at least a 2-week delay in treatment. We suggest that in general, hematomas do not require much intervention. Compressive wraps and reassurance are often enough, especially in lower-grade asymptomatic cases. However, drainage may be necessary to alleviate pain and discomfort for blood blisters. We recommend delay in treatment due to associated swelling/edema, which may worsen discomfort with injections or make the plaque difficult to palpate for appropriate delivery of the medication. In the setting of higher-grade hematomas, it is important to consider the possibility of corporal rupture.

Corpora cavernosa rupture

Corpora cavernosa rupture, or "penile fracture," is the most severe complication related to CCH. With a similar mechanism to that causing hematomas, rupture of the corpora cavernosa can be caused by full-thickness degradation of the tunica albuginea or by tearing at a weakened section when subject to intense sexual activity.[16] It should be suspected when larger hematomas are present, and clinicians should evaluate for suggestive history, such as occurrence during intercourse, a "pop" or "crackling" sound, and detumescence. When history is equivocal, ultrasound or, ideally, magnetic resonance imaging can aid in confirming the diagnosis. Corporal rupture should still be considered in the correct clinical context even 2 weeks following injection, as late-onset rupture can occur in up to 80% of the cases.[21] Most experts recommend managing corporal rupture conservatively as opposed to surgical exploration and repair of the corpora, as performed for traumatic corporal rupture outside the context of CCH.[22] In case of concomitant urethral injury, penile fracture should still be repaired surgically, as delayed surgical repair has demonstrated worse outcomes in this scenario.[21]

Other considerations

The use of blood thinners was not associated with higher hematoma rates in a 2020 cohort with 183 patients.[23] Men taking antiplatelet agents or anticoagulants during their CCH injections (17% of the cohort) did not have increased complication rates as compared with the group that was not using any blood-thinning medications.

High dropout rates from CCH treatment for PD, ranging from 13% to 56%, were reported in several articles in the literature. Dissatisfaction with therapy is the most common reason for discontinuation. However, complications should be considered an important factor in those cases. Amighi et al reported hematoma formation as a predictor of dropout in their cohort.[24]

Although there is a concern for complications with CCH therapy, it is important to note that adverse consequences of the treatment do not appear to hinder efficacy. Walker et al published evidence that major TRAEs do not affect efficacy as compared with no TRAEs.[25] This study, however, had its limitations, as no corporal rupture was observed in their sample.

Conclusions

Recognizing and grading complications associated with CCH therapy for PD is crucial for effective patient management and informed decision making. A standardized grading system allows for consistency in reporting and comparing hematoma complication rates across studies and patient populations. Herein, we provide images that will help clinicians identify and confidently manage common complications that may occur in any CCH program.

Author contributions

T.P.F.: writing. V.O., J.J.A., S.V.E.: editing. J.N.M.: supervision, conceptualization.

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Conflict of interest

J.N.M. is a consultant for Halozyme Pharma, Boston Scientific, and Endo Pharmaceuticals. All other authors declare no competing interests.

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