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Unsafe Care and Misunderstanding Diagnosis in Freeman-Burian syndrome: Problems in Writing Case Reports Involving Rare Conditions and Strategies for Improvement

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Abstract

For rare conditions, avoiding hastily publishing case reports, conducting a thorough literature search, and ensuring the patient's presentation aligns with accepted diagnostic criteria are each essential. Failure to heed the above can lead to serious inaccuracies, as illustrated by four articles we reviewed in the past year.

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Freeman-Burian syndrome; Freeman-Sheldon syndrome; malignant hyperthermia; craniocarpotarsal dystrophy; whistling face syndrome; distal arthrogryposis type 2A; case reports; rare diseases; craniofacial abnormalities

INTRODUCTION

We read with great interest the article by Sato Boku, Sento, Hasegawa, Tsutsumi, Kamimura, So, Kako, and Sobue, "Anesthetic management of a patient with Freeman-Sheldon syndrome undergoing oral surgery: a case report."[1-2] It is encouraging to see this exquisitely rare condition discussed in the literature. Unfortunately, this article[1-2] contains significant flaws (Fig 1), apparently resulting from the authors' omission of recent literature, especially clinical recommendations for anesthesia management.[3-8] As Freeman-Sheldon syndrome, now Freeman-Burian syndrome (FBS),[9] is an exquisitely rare condition, little is known about it. Many who believe they have encountered it in clinical practice are eager to publish their experience, despite the perils.

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Authors' Error	Rationale
Reference list	• Lack of recent references, including: articles on the genetic cause, clinical diagnosis, a meta-analysis, anesthesia recommendations, etc.
"reported prevalence than 1 per 1 million"	• Based on one flawed study and no longer accepted. Poor writing.
"multiple joint contractures, characteristic facial features, such as microtia, defects of the hands and feet, such as clubfoot, and skeletal malformations"	• Joint contractures and extremity deformities are non-specific findings. • Only the four craniofacial findings of microstomia, pursed whistling lips, deep nasolabial folds, and H or V shaped chin defect are pathognomonic for FBS. • FBS is a myopathy, not skeletal condition. • Microtia is not seen in FBS.
Omission of the clinical diagnostic criteria	• Not stating the diagnostic criteria confuses the reader unfamiliar with FBS.
"association with malignant hyperthermia [MH]," and FBS	• MH is not associated with FBS.
"Reports on the general anesthetic management of FSS patients have been disorganized..."	• Fails to mention meta-analysis or clinical practice recommendations
Omission of photographs or a description of how the patient met the diagnostic criteria	• Stating the patient had FBS is insufficient, considering the false positive rate may be between 30-60%.
General anesthesia would cause, "worsening of respiratory insufficiency and postoperative pneumonia."	• Good anesthesia care avoids both.
The authors considered four options: local anesthesia, local anesthesia with narcotic analgesia, local anesthesia with sedation, and general endotracheal anesthesia.	• The two safe options are local anesthesia only and general endotracheal anesthesia. • Sedation without a secure airway should not happen, as dysphagia, pulmonary complications (especially aspiration pneumonia), and difficult airway are all major problems in this patient population. • While respiratory depression can be exacerbated with opiates, short-acting opiates have been safely used.
The authors considered three concerns involving general endotracheal anesthesia: difficult intubation, "respiratory failure", and risk of MH.	• Difficult intubation is a major challenge in FBS but not a contraindication. • "Respiratory failure" should never be a likely event with good care. • Respiratory depression is a greater concern in FBS but can be prevented. • MH is not associated with FBS.
"causes respiratory decline in adults"	• No evidence of decline or (if present) of FBS as a primary cause.
"respiratory muscle fatigue"	• Primary muscle fatigue is not part of FBS.
"There was no facial deformity or limitation of retroflexion in this case."	• Craniofacial deformities are required for FBS diagnosis.
"Although NHF was not used in this case, it may have been useful..."	• Anatomic infeasibility due to narrowed nasopharynx

Figure 1: Major errors in case report of Freeman-Burian syndrome published in June 2021 and rationale.

While there is always merit in discussing FBS, care must be taken to ensure the most current and accurate information is reviewed. In FBS, most facts repeated as true are, in fact, false. Within the past year, we have encountered and responded to four case reports harboring fundamental and clinically dangerous errors in diagnosis and treatment in FBS.[1-2,10-15] In discussing this recent article,[1-2] we highlight six errors shared among the four manuscripts (Fig 2) and suggest methods (Fig 3) to avoid potentially harmful inaccuracies for both FBS and other exceptionally rare conditions.

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Authors' Error	Rationale
Reference list	• Lack of recent references, including: articles on the genetic cause, clinical diagnosis, a meta-analysis, anesthesia recommendations, etc.
Statement of a prevalence of 1:1 million	• Based on one flawed study and no longer accepted
Description of the syndrome as having multiple joint contractures, characteristic facies, clubfoot, and various hand deformities	• Joint contractures and extremity deformities are non-specific findings. • Only the four craniofacial findings of microstomia, pursed whistling lips, deep nasolabial folds, and H or V shaped chin defect are pathognomonic for FBS.
Classification of FBS as either a distal arthrogryposis or skeletal condition	• FBS is primarily a craniofacial condition with frequent findings outside the craniofacial region. • FBS is a myopathy, not distal arthrogryposis or skeletal condition.
Omission of the clinical diagnostic criteria	• Not stating the diagnostic criteria confuses the reader unfamiliar with FBS.
Omission of photographs or a description of how the patient met the diagnostic criteria	• Stating the patient had FBS is insufficient, considering the false positive rate may be between 30-60%.

Figure 2: Common major errors in case reports purportedly describing patients with Freeman-Burian syndrome from 2020-2021 and rationale.

Recommendations
Follow CARE guidelines
Identify as many of the following types of published articles as possible: most recent narrative review, most recent meta-analysis, any clinical practice recommendations, studies showing a molecular or genetic cause, reports of an accepted diagnostic criteria, descriptions of treatment
Carefully compare the diagnostic criteria with the patient's data
Only describe patients all authors have seen in person
Consult an expert on the rare condition, and provide access to appropriate materials to that individual
The manuscript should outline the diagnostic criteria and objectively demonstrate how the patient met them
The manuscript should follow logically within a known disease mechanism or cautiously propose a new one

Figure 3: Recommendations for creating improved case reports describing very rare conditions.

REVIEW OF MANUSCRIPT

The authors', while seemingly well-intentioned and methodical, have made a number of concerning errors (Fig 1), all of which could have been avoided by a more careful search of recent literature on FBS. For example, the authors omitted the two seminal articles that defined the clinical and genetic diagnosis,[16-17] molecular physiology,[18-20] the only meta-analysis on FBS,[3] and the clinical practice recommendations for anesthesia care.[8] Unfortunately, the authors cite[1-2] only one recent article, which was one of four published over the past year that were deeply flawed[10] and to which we responded[13] in a letter to the editor. Conducting a sound literature search is not restricted to the preserve of academics. The present article in question[1-2] brings into sharp relief the connection between the quality of a literature search and clinical reasoning displayed in patient care.

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The authors cite[1-2] the unsubstantiated frequency of 1:1 million, which was based on a single retrospective study of patients in the UK having skeletal dysplasias and included FBS.[21] FBS is often misdiagnosed, making it academically irresponsible to accept a recorded FBS diagnosis without objective patient data.[3] This study's frequency for FBS is no longer accepted, and the prevailing estimate is that 200-300 individuals worldwide may have FBS.[4]

The authors describe patients as having, "multiple joint contractures, characteristic facial features, such as microtia, defects of the hands and feet, such as clubfoot, and skeletal malformations."[1-2] External ear position variances may be seen in FBS, but microtia is not seen in FBS.[3] Otherwise, the description is mostly true for most patients, while remaining very misleading. Only the craniofacial features (microstomia, pursed whistling lips, deep nasolabial folds, and H or V-shaped chin defect) required in the diagnostic criteria are pathognomonic for FBS.[3,16-17] Distal extremity contractures are a non-diagnostic finding in FBS and common in many syndromic and non-syndromic entities.[3-4,16] The authors also do not state[1-2] the accepted clinical diagnostic criteria[16] that have been shown to be strongly correlated with molecular diagnosis[17]. Not directly stating the diagnostic criteria, as the authors failed to do,[1-2] can confuse the reader unfamiliar with FBS.

Furthermore, FBS is a congenital craniofacial syndrome of myopathic origin that frequently involves findings outside the craniofacial region (spine and extremities), though FBS has had many classifications since its first description in 1938 and independent confirmation in 1962.[22-24] In the syndrome, "skeletal malformations" are secondary effects of the primary myopathic process of fibrose tissue replacement of normal muscle fibers.[4] This fibrose tissue acts as constricting bands, the way collagen behaves in severe burns.[4] These findings are consistent with *in vitro* molecular myophysiology observations showing problems with the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power.[18-20] Misunderstanding of etiology in FBS has led to inappropriate treatment plans, especially surgeries, and has resulted in tragic, lifelong impairments.[3-5]

The authors referred to a risk of, "association with malignant hyperthermia (MH)," and FBS.[1-2] The potential association of MH and FBS was based on a single report of two cases.[25] Some patients with FBS do, indeed, develop hyperpyrexia during general anesthesia, but it has also been observed to be resolved by administration of ibuprofen.[8] These hyperpyrexia events, which may include tachycardia and increased muscle rigidity, have also been seen in settings where an MH protocol was followed and in non-operative stress situations, such as physical or mental stress well beyond what the individual typically experienced.[8] It seems, then, these hyperpyrexia events may not represent true MH events.[8]

The authors write that, "Reports on the general anesthetic management of FSS patients have been disorganized."[1-2] While it is true that anesthesia case reports have been spotty and of varying quality, this is not a unique phenomenon.[3] There are only two published studies of FBS, neither of which addressed anesthesia in any detail.[16-17] There is, however, a meta-analysis of individual patient data extracted from rigorously evaluated case reports and anesthesia clinical practice recommendations.[3,8] Both of these articles consolidate the evidence-base for anesthesia care of FBS patients in detail.[3,8]

Without photographs or a detailed description of how the patient met the diagnostic criteria, it is not certain the patient described had FBS. Stating the patient had FBS is insufficient, considering the false positive rate may be between 30-60%.[3] Near the end of the article, the authors remark that, "There was no facial deformity... in this case,"[1-2] making it rather unlikely the patient described had FBS. Four main craniofacial deformities (microstomia, pursed whistling lips, deep nasolabial folds, and H or V-shaped chin defect) are required for diagnosis,[3,16-17] and all patients present with an assortment of additional common but not required craniofacial stigmata.[3,6]

The authors assert that general anesthesia would cause, "worsening of respiratory insufficiency and post-operative pneumonia."[1-2] Though the risk is greater for post-operative respiratory complications in FBS patients, general anesthesia certainly does not directly cause post-operative respiratory distress and pneumonia.[8] Nonetheless, patients require care from experienced providers, ideally in tertiary referral centers.[8]

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Astute anesthesia and post-anesthesia care for patients with FBS, as outlined in the clinical practice recommendations, is specifically directed toward avoiding post-operative respiratory sequelae.[8]

The authors considered four options: local anesthesia, local anesthesia with narcotic analgesia, local anesthesia with sedation, and general anesthesia.[1-2] Expressly because of the need to ensure a secure airway to prevent aspiration pneumonia, the two safe options are local anesthesia only, where the patient is fully alert without impaired cognition and able to protect their own airway; and general anesthesia, where the patient's airway is secured via orotracheal intubation or a surgical airway.[7-8] The authors acknowledged the pulmonary concerns[1-2,26] but paradoxically wished to avoid invasive airway management in a sedated patient undergoing oral surgery, which is a major risk to patient safety in FBS and should not happen.[1-2] Local anesthesia with narcotic analgesia would not be an option either. As correctly observed by the authors, respiratory depression can be exacerbated with opiates, but short-acting options exist and have been safely used in this syndrome.[8] The bigger risk is the cognitive effect of the narcotics when used in an awake FBS patient for procedural pain control for oral surgery.[7-8]

The authors next outline three concerns they have with general anesthesia, including: difficult intubation, "respiratory failure", and risk of MH.[1-2] They seemingly present these as justification for considering general anesthesia to be contraindicated in FBS or at least in their case.[1-2] Difficult intubation is a major challenge in FBS requiring considerable skill but is not insurmountable.[8] The other two concerns are flatly illogical. "Respiratory failure" should never be a likely event with good care.[8] Respiratory depression is a greater concern in FBS but as described above, one of the major goals of anesthesia care is to prevent it.[8] As mentioned above, MH is not associated with FBS.[8]

The authors write, "[FBS] causes respiratory decline in adults."[1-2] There is no evidence supporting either a decline in respiratory function or of FBS being a primary cause in any decline observed. While FBS may limit healthy physical activity necessary for maintaining respiratory function status, lifestyle and ageing are expected to be main contributors to any observed decline, as they would be in the general population.[5] The authors also refer to, "respiratory muscle fatigue."[1-2] As discussed previously, FBS results in the formation of white fibrous tissue constricting bands within normal muscle and complete muscle replacement by white fibrous tissue.[4] Primary muscle fatigue is not part of FBS.

Finally, the authors consider nasal high-flow (NHF) oxygen cannulae in FBS and write, ""Although NHF was not used in this case, it may have been useful. . . ."[1-2] Though NHF has an important role in critical care and other settings, its use in this patient population probably would be impractical, due to anatomically restricted airflow in the nasopharynx of most FBS patients that would preclude efficient oxygenation. For this reason, nasal airways and nasal intubation also are ineffective airway management methods in many FBS patients. Orotracheal intubation or a surgical airway are the most reliable techniques for providing effective airway protection and positive-pressure support.[8]

DISCUSSION

While undoubtedly well-intentioned, the article by Sato Boku, Sento, Hasegawa, Tsutsumi, Kamimura, So, Kako, and Sobue illustrates the scholarly outcome of an insufficient literature search.[1-2] Had the authors carried out a more complete search and review, all of the subsequent errors could have been avoided, a failing common to the other three case reports we have reviewed in the last year purportedly describing patients with FBS (Fig 2). Below we discuss specific steps we have identified that, had they been followed, would have provided multiple levels of safeguards to ensure the most accurate information was presented in each of these four case reports (Fig 3).

When conducting a literature search while considering whether to write a case report of a patient with a rare condition, it is particularly important to try to find and carefully read as many of the following as possible: most recent narrative review, most recent meta-analysis, any clinical practice recommendations, studies showing a molecular or genetic cause, reports of an accepted diagnostic criteria, and descriptions of treatment. Reviewing only case reports, especially older articles, led the authors of the four articles we reviewed to incorrect conclusions.[1-2,10-15] While high-quality randomized controlled trials and large

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observational studies are unlikely to be found for many rare conditions, carefully reading a variety of published article types should help potential authors.

Just as journals have required manuscript compliance with CONSORT, STROBE, and PRISMA guidelines when reporting randomized trials, observational studies, and systematic reviews, journals that accept case reports have begun requiring case report manuscript adherence to the CARE guideline, which provides a logical framework for reporting case reports.[27-30] This should be considered a minimum standard and is not specific for rare conditions.

The most important safeguard, however, is to consider that writing case reports about rare conditions in patients is fundamentally different from almost any other circumstance. If describing a patient with diabetes mellitus, it would almost always be considered redundant to describe why the patient was diagnosed with diabetes mellitus. It's a common condition, and the audience of any medical journal would neither need nor wish to see this information to be satisfied the patient was correctly diagnosed. For a rare condition, where neither the majority of authors nor audience would be expected to be experts, objectively establishing the diagnosis in the context of the accepted criteria for diagnosis is paramount. The cogency of the entire case report depends on having established an accurate diagnosis.

Authors should have personally seen the patient and be familiar with their history, presentation, and care to improve accuracy and precision in reporting. Experts in the rare condition should be consulted and provided as much medical data as possible. They also should review the manuscript to evaluate the accuracy of the case presentation and discussion. It is not thought to be necessary that the consulting expert sees the patient.

Finally, any resulting manuscript should clearly present how the patient's presentation matched the accepted diagnostic criteria and generally follow logically within a known disease mechanism or very cautiously propose a new one. As with all manuscripts, authors should strive to interpret the relevance of their case and how their case report may point toward future needed research. In the context of rare conditions, this may not be as straightforward and require extra consideration.

Conclusion

FBS is an incredibly rare condition, and the article evaluated[1-2] illustrates the perils of describing a rare condition. Careful review of four published case reports from 2020-2021[1-2,10-15] purportedly describing patients with FBS reveals six common errors (Fig 2), chief of which was an inadequate literature search that caused the authors to draw erroneous conclusions, i.e. reporting fake news. The lack of improvement in care, since its first description in 1938, is a testament to the outsized deleterious clinical impact poor case reports can have in rare conditions,[3-5] and potential authors bear ultimate responsibility for guiding improvements in patient care by conscientious writing. Following a few mutually-supporting steps (Fig 3), authors can improve the accuracy and precision of case reports involving patients with rare conditions and guide the global improvement of care for these patients.

REFERENCES

1. Sato Boku A, Sento Y, Hasegawa T, Tsutsumi K, Kamimura Y, So M, Kako E, Sobue K. Anesthetic management of a patient with Freeman-Sheldon syndrome undergoing oral surgery: a case report. Clin Case Rep. 2021;9(6):e04358. Published 2021 Jun 9. doi: 10.1002/ccr3.4358
2. Sato Boku A, Sento Y, Hasegawa T, Tsutsumi K, Kamimura Y, So M, Kako E, Sobue K. Anesthetic management of a patient with Freeman-Sheldon syndrome undergoing oral surgery: A case report. Authorea. April 13, 2021. doi: 10.22541/au.161831534.42337279/v1
3. Poling MI, Dufresne CR, Chamberlain RL. Findings, Phenotypes, Diagnostic Accuracy, and Treatment in Freeman-Burian Syndrome. J Craniofac Surg. 2020;31(4):1063-1069. doi: 10.1097/SCS.0000000000006299
4. Poling MI, Dufresne CR, Chamberlain RL. Freeman-Burian syndrome. Orphanet J Rare Dis. 2019;14(1):14. doi: 10.1186/s13023-018-0984-2

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5. Poling MI, Dufresne CR, McCormick RJ. Identification and Recent Approaches for Evaluation and Management of Rehabilitation Concerns for Patients with Freeman-Burian Syndrome: Principles for Global Treatment. J Ped Genet. 2020;09(03):158-163. doi: 10.1055/s-0040-1710339
6. Poling MI, Dufresne CR, Portillo AL. Identification and recent approaches for evaluation, operative counseling, and management in patients with Freeman-Burian syndrome: principles for global treatment. J Craniofac Surg. 2019;30(8):2502–2508. doi: 10.1097/SCS.0000000000005968
7. Poling MI, Dufresne CR. Identification and Recent Approaches for Evaluation and Management of Dentofacial and Otolaryngologic Concerns for Patients With Freeman-Burian Syndrome: Principles for Global Treatment. J Craniofac Surg. 2020;31(3):787-790. doi: 10.1097/SCS.0000000000006155
8. Poling MI, Dufresne CR. Freeman-Burian syndrome. Anästh Intensivmed. 2019;60(1):S8-S17. doi: 10.19224/ai2019.S008
9. Poling MI, Dufresne CR. Revisiting the many names of Freeman-Sheldon syndrome. J Craniofac Surg. 2018;29(8):2176–2178. doi: 10.1097/SCS.0000000000004802
10. Kamal G, Shah SB, Gupta A. Anesthesia Challenges in the Management of Freeman-Sheldon Syndrome: Report of Two Cases and Literature Review. AANA J. 2020;88(1):35-38. PMID: 32008616.
11. Park J, Kang SW, Choi WA, Lee Y, Cho HE. Precise Pulmonary Function Evaluation and Management of a Patient With Freeman-Sheldon Syndrome Associated With Recurrent Pneumonia and Chronic Respiratory Insufficiency. Ann Rehabil Med. 2020;44(2):165-170. doi: 10.5535/arm.2020.44.2.165
12. Wróblewska-Seniuk K, Jarząbek-Bielecka G, Kędzia W. Freeman-Sheldon syndrome - a course of the disease from birth to adulthood. Clin Exp Obstet Gynecol. 2020;47(6): 978-982.
13. Poling MI, Dufresne CR. Letter. AANA J. 2020;88(5):54.
14. Poling MI, Dufresne CR. Letter: Precise Pulmonary Function Evaluation and Management of a Patient With Freeman-Sheldon Syndrome Associated With Recurrent Pneumonia and Chronic Respiratory Insufficiency. Ann Rehabil Med. 2020;44(5):409-410. doi: 10.5535/arm.20110
15. Poling MI, Dufresne CR. Accuracy of Facts About Freeman-Sheldon syndrome. Clin Exp Obstet Gynecol. 2021;48(5):997-998.
16. Stevenson DA, Carey JC, Palumbos J, Rutherford A, Dolcourt J, and Bamshad MJ. Clinical characteristics and natural history of Freeman-Sheldon syndrome. Pediatrics. 2006;117 (3):754-762. doi: 10.1542/peds.2005-1219
17. Toydemir RM, Rutherford A, Whitby FG, Jorde LB, Carey JC, Bamshad MJ. Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Nat Genet. 2006;38(5):561-5. doi: 10.1038/ng1775
18. Racca AW, Beck AE, McMillin MJ, Korte FS, Bamshad MJ, Regnier M. The embryonic myosin R672C mutation that underlies Freeman-Sheldon syndrome impairs cross-bridge detachment and cycling in adult skeletal muscle. Hum Mol Genet. 2015;24(12):3348-58. doi: 10.1093/hmg/ddv084
19. Bell KM, Kronert WA, Guo Y, Rao D, Huang A, Bernstein SI, and Swank DM. The muscle mechanical basis of Freeman-Sheldon syndrome. Biophysical J. 2016;110(3):14a.
20. Walklate J, Vera C, Bloemink MJ, Geeves MA, Leinwand L. The most prevalent Freeman-Sheldon syndrome mutations in the embryonic myosin motor share functional defects. J Bio Chem. 2016;291(19):10318-10331. d oi: 10.1074/jbc.M115.707489
21. Wynne-Davies R, Gormley J. The prevalence of skeletal dysplasias: an estimate of their minimum frequency and the number of patients requiring orthopaedic care. J Bone Joint Surg Br. 1985;67-B(1):133-137. PMID: 3155744.
22. Poling MI, Dufresne CR. Head first, not feet first: Freeman-Sheldon syndrome as primarily a craniofacial condition. Cleft Palate-Craniofac J. 2018;55(5):787-788. doi: 10.1177/1055665617753482
23. Freeman EA, Sheldon JH. Cranio-carpo-tarsal dystrophy: undescribed congenital malformation. Arch Dis Child. 1938;13:277-283. doi: 10.1136/adc.13.75.277
24. Burian F. [The "whistling face" symptom in the polyvalent syndrome]. Acta Chir Orthop Traumatol Cech. 1962;29:481-483. PMID: 14017018.
25. Jones R, Dolcourt JL. Muscle rigidity following halothane anesthesia in two patients with Freeman-Sheldon syndrome. Anesthesiology. 1992;77(3):599-600. doi: 10.1097/00000542-199209000-00031

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26. MacLeod P, Patriquin H. The whistling face syndrome—cranio-carpo-tarsal dysplasia. Report of a case and a survey of the literature. Clin Pediatr (Phila). 1974;13(2):184-9. d oi: 10.1177/000992287401300213
27. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-732. doi: 10.7326/0003-4819-152-11-201006010-00232
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [published correction appears in Ann Intern Med. 2008 Jan 15;148(2):168]. Ann Intern Med. 2007;147(8):573-577. doi: 10.7326/0003-4819-147-8-200710160-00010
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Published 2021 Mar 29. doi: 10.1136/bmj.n71
30. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. BMJ Case Rep. 2013;2013:bcr2013201554. Published 2013 Oct 23. doi: 10.1136/bcr-2013-201554