

CARE guidelines for case reports: explanation and elaboration document

David S. Riley^{a,*}, Melissa S. Barber^b, Gunver S. Kienle^c, Jeffrey K. Aronson^d,
Tido von Schoen-Angerer^e, Peter Tugwell^f, Helmut Kiene^g, Mark Helfand^h, Douglas G. Altmanⁱ,
Harold Sox^j, Paul G. Werthmann^g, David Moher^k, Richard A. Rison^l, Larissa Shamseer^k,
Christian A. Koch^m, Gordon H. Sunⁿ, Patrick Hanaway^o, Nancy L. Sudak^p,
Marietta Kaszkin-Bettag^q, James E. Carpenter^r, Joel J. Gagnier^{s,t}

^aIntegrative Medicine Institute, 2437A NW Overton Street, Portland, OR 97210, USA; Helfgott Research Institute, 2220 SW 1st Ave, Portland, OR 97201, USA

^bIntegrative Medicine Institute, 2437A NW Overton Street, Portland, OR 97210, USA

^cSenior Research Scientist, University of Freiburg, Fahrenbergplatz, 79085 Freiburg im Breisgau, Germany; Senior Research Scientist, Institute for Applied Epistemology and Medical Methodology at the University of Witten-Herdecke, Zechenweg 6, 79111 Freiburg im Breisgau, Germany

^dUniversity of Oxford, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK

^eDepartment of Pediatrics, Centre médical de La Chapelle, Chemin de Compostelle 7, 1212 Grand-Lancy, Genève, Switzerland; ACIM Institute, Filderklinik, Im Haberschlag 7, 70794 Filderstadt-Bonlanden, Germany

^fDepartment of Medicine University of Ottawa, 451 Smyth Rd, Ottawa, ON, Canada K1H 8M5

^gSenior Research Scientist, Institute for Applied Epistemology and Medical Methodology at the University of Witten-Herdecke, Zechenweg 6, 79111 Freiburg im Breisgau, Germany

^hDepartment of Medical Informatics and Clinical Epidemiology, 3710 SW US Veterans Hospital Rd, Portland, OR 97239, USA

ⁱUniversity of Oxford, Center for Statistics - Botnar Research Centre, Windmill Road, Oxford OX3 7LD, UK

^jProfessor Medicine and of The Dartmouth Institute, Geisel School of Medicine at Dartmouth, 31 Faraway Lane, West Lebanon, NH 03784-4401, USA

^kSenior Scientist, Ottawa Methods Centre, Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, ON, Canada K1H 8L6

^lPIH Health Hospital-Whittier, Neurology Consultants Medicine Group, University of Southern California Keck School of Medicine, 12291 Washington Blvd # 303, Whittier, CA 90606, USA

^mProfessor of Medicine, Director - Endocrinology at the University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216, USA

ⁿMedical Director of Inpatient Services at Rancho Los Amigos National Rehabilitation Center, 7601 Imperial Highway, Downey, CA 90242, USA

^oCenter for Functional Medicine, Cleveland Clinic, Mail Code H-18, 9500 Euclid Avenue, Cleveland, OH, 44195, USA

^pEssentia Health - Duluth, 420 East First Street, Duluth, MN 55805-1951, USA

^qDirector of Scientific Affairs - PharmaLex, Harrlachweg 6, 68163 Mannheim, Germany

^rDepartment Chair, Orthopaedic Surgery, 24 Frank Lloyd Wright Drive, Lobby A, Ann Arbor, MI 48106, USA

^sDepartment of Orthopaedic Surgery, 24 Frank Lloyd Wright Drive, Lobby A, Ann Arbor, MI 48106, USA

^tDepartment of Epidemiology, School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109-2029, USA

Accepted 27 April 2017; Published online 18 May 2017

Abstract

Background: Well-written and transparent case reports (1) reveal early signals of potential benefits, harms, and information on the use of resources; (2) provide information for clinical research and clinical practice guidelines, and (3) inform medical education. High-quality case reports are more likely when authors follow reporting guidelines. During 2011–2012, a group of clinicians, researchers, and journal editors developed recommendations for the accurate reporting of information in case reports that resulted in the CARE (CASE REport) Statement and Checklist. They were presented at the 2013 International Congress on Peer Review and Biomedical Publication, have been endorsed by multiple medical journals, and translated into nine languages.

Objectives: This explanation and elaboration document has the objective to increase the use and dissemination of the CARE Checklist in writing and publishing case reports.

Funding: The 2012 CARE consensus meeting in Ann Arbor, Michigan, received funding from the Department of Orthopedic Surgery, the Office of the Executive Vice President of Research from the University of Michigan, Ann Arbor, Michigan, and Global Advances in Health and Medicine (grant number: 201210-3). CARE planning and working group meetings have been hosted by the University of Ottawa, Ottawa, CA (D.M. is supported by a University Research Chair, University of Ottawa); Integrative

Medicine Institute, Portland, Oregon; and the Institute for Applied Epistemology and Methodology at the University of Witten/Herdecke in Freiburg, Germany. No funding, direct or indirect, was received to write this article.

* Corresponding author. Tel.: +505 690-0688; fax: +503 227-3750.
E-mail address: dsriley@care-statement.org (D.S. Riley).

Article Design and Setting: Each item from the CARE Checklist is explained and accompanied by published examples. The explanations and examples in this document are designed to support the writing of high-quality case reports by authors and their critical appraisal by editors, peer reviewers, and readers.

Results and Conclusion: This article and the 2013 CARE Statement and Checklist, available from the CARE website [www.care-statement.org] and the EQUATOR Network [www.equator-network.org], are resources for improving the completeness and transparency of case reports. © 2017 Elsevier Inc. All rights reserved.

Keywords: Case report; Case study; EQUATOR network; Health research reporting guidelines; CARE guideline; Timelines; N-of-1

1. Introduction

Case reports describe a patient's medical problems and clinical management for scientific or educational purposes. Historically, case reports have been important in (1) recognizing new or rare diseases, (2) evaluating the beneficial and harmful effects of an intervention, and (3) medical education [1,2]. They comprise a significant proportion of the articles in many indexed medical journals—case report volume, indexed on EMBASE and MEDLINE, increased by 45% from 49,918 in 2000 to 72,388 in 2010 [3]. New medical report journals focusing on case reports have emerged in the past 10 years, some from publishers who have been labeled “predatory publishers” [4]. Most are open access, and others are “supplements” or “companions” to established medical journals, such as *Neurology Clinical Practice*, a companion journal to *Neurology* from the American Academy of Neurology. Table 1 is a partial list of peer-reviewed journals that explicitly accept case reports.

1.1. Medical journal—case reports table about here or as an appendix

Seminal examples published in the past 60 years illustrate how cases reported in the peer-reviewed medical literature have broadened our knowledge of emerging or existing conditions and their management. In 1961, *The Lancet* published a letter to the editor describing an increased incidence of congenital abnormalities in babies delivered of women who were given thalidomide during pregnancy as an antiemetic or sedative [5]. The *Morbidity and Mortality Weekly Report* published five case reports of *Pneumocystis carinii* pneumonia (PCP) in 1981 that turned out to be early signals of AIDS [6]. The *Journal of Medical Case Reports* in 2013 reported that women who suffer a stroke may have May-Thurner syndrome, a condition affecting nearly 1 in 2,000 women [7]. And in 2016, the *New England Journal of Medicine* published a report on Zika virus infection that included a case report of a patient with prolonged maternal viremia and fetal brain abnormalities—serologic evidence of infection [8].

1.2. Improving the quality of case reports

The usefulness of case reports has been limited by inconsistent and incomplete reporting. When written without reporting guidelines, they are often insufficiently rigorous [9] and fail to provide information related to

clinical management that would increase transparency and the likelihood of replication [10].

In 2011, a group of clinicians, researchers, and journal editors developed reporting guidelines for case reports following guideline development recommendations [11]. This process consisted of (1) a literature review, interviews, using a modified Delphi process to generate items for a case report checklist, (2) a consensus meeting to draft reporting guidelines for case reports, and (3) a postmeeting evaluation, finalization, and publication of the reporting guidelines for case reports [12]. The 2013 CARE Statement and Checklist were presented at the 2013 International Congress on Peer Review and Biomedical Publication, published in and endorsed by multiple medical journals, and translated into nine languages. The objective of this document is to support the publication of accurate, complete, and transparent case reports.

1.3. Using this document

Each CARE Checklist item is explained and accompanied by one or more illustrative examples to guide case report writing and their critical appraisal by editors, peer reviewers, and readers. Familiarity with reporting guidelines form part of the foundation of editorial competency and the critical appraisal of manuscripts by medical journal editors and peer reviewers [13].

This document and the CARE statement (available at www.care-statement.org) are resources to improve the quality of case reports. With the CARE Checklist as a framework, the writing of case reports continues to be an art, allowing author choices in focusing the case, sharing a patient's story in a way that appeals to readers and provides information for scientific and educational purposes.

2. The CARE Checklist

The 2013 CARE Checklist (see Fig. 1) provides a framework for writing case reports that can be adapted to include specialty-specific information.

2.1. The CARE Checklist—explanation and elaboration

In this section, each of the CARE Checklist items and subitems are explained, accompanied by examples from peer-reviewed, general, and specialty medical journals.

What is new?

- This article serves as a “users manual” to accompany the CARE guidelines and checklist, providing guidance for authors and medical journals in the writing and critical appraisal of case reports. The CARE groups believe that case reports have the potential to offer early signals from the point of care that can be useful for clinical research, inform clinical practice guidelines, and improve medical education. The CARE guidelines have been translated into 10 languages and endorsed by many medical journals.

phenomenon of greatest interest (e.g., symptoms, diagnoses, tests, interventions)

2.2.1. Explanation

The title should be succinct and help readers clearly identify the focus of the case report (e.g., medical condition, intervention, outcome, population). It is useful if the article is identified as a case report [15]. This facilitates indexing in databases and may improve search results. “Case reports” are in MeSH (Medical Subject Headings—available at www.pubmed.com), a National Library of Medicine controlled vocabulary thesaurus used for indexing articles included in MEDLINE.

2.2. Item 1. Title section

CARE Checklist description: The words “case report” (or “case study”) should appear in the title along with

2.2.2. Example

“Successful heart transplantation after 13 hours of donor heart ischemia with the use of HTK solution: a case report” [16].

The narrative: A case report tells a story in a narrative format that includes the presenting concerns, clinical findings, diagnoses, interventions, outcomes (including adverse events), and follow-up. The narrative should include a discussion of the rationale for any conclusions and any take-away messages.

Section	Item number	Item description
Title	1	The words “case report” (or “case study”) should be in the title along with phenomenon of greatest interest (e.g., symptom, diagnosis, test, intervention)
Keywords	2	The key elements of this case in 2–5 words.
Abstract	3	a) Introduction—What does this case add? b) Case presentation: – The main symptoms of the patient – The main clinical findings – The main diagnoses and interventions – The main outcomes c) Conclusion—What were the main “take-away” lessons from this case?
Introduction	4	Brief background summary of the case referencing the relevant medical literature.
Patient information	5	a) Demographic information of the patient (age, gender, ethnicity, occupation) b) Main symptoms of the patient (his or her chief complaints) c) Medical, family, and psychosocial history—including diet, lifestyle, and genetic information whenever possible and details about relevant comorbidities and past interventions and their outcomes
Clinical findings	6	Describe the relevant physical examination (PE) findings
Timeline	7	Depict important dates and times in the case (table or figure)
Diagnostic assessment	8	a) Diagnostic methods (e.g., PE, laboratory testing, imaging, questionnaires) b) Diagnostic challenges (e.g., financial, language/cultural) c) Diagnostic reasoning including other diagnoses considered d) Prognostic characteristics (e.g., staging) where applicable
Therapeutic interventions	9	a) Types of intervention (e.g., pharmacologic, surgical, preventive, self-care) b) Administration (e.g., dosage, strength, duration) c) Changes in intervention (with rationale)
Follow-up and outcomes	10	a) Clinician and patient-assessed outcomes b) Important follow-up test results (positive or negative) c) Intervention adherence and tolerability (and how this was assessed) d) Adverse and unanticipated events
Discussion	11	a) Strengths and limitations of the management of this case b) Relevant medical literature c) Rationale for conclusions (including assessments of cause and effect) d) Main “take-away” lessons of this case report
Patient perspective	12	The patient should share their perspective or experience whenever possible.
Informed consent	13	Did the patient give informed consent? Please provide if requested.

Table 1. Partial list of medical journals that explicitly accept case reports

Journal title ^a	Indexed	Publisher
1. ACG Case Reports journal	PMC	American College of Gastroenterology
2. Acta Radiologica Open	PMC	Sage
3. Advances in Integrative Medicine ^b	Scopus	Elsevier
4. AHRQ WebM&M	psnet.ahrq.gov/webmm	AHRQ
5. Alternative Therapies in Health and Medicine ^b	IF, MEDLINE, Scopus	Innovision Health Media
6. American Journal of Case Reports	MEDLINE, PMC, Scopus	International Scientific Information
7. American Journal of Ophthalmology Case Reports	Scopus	Elsevier
8. American Journal of Perinatology (AJP) Reports	PMC	Thieme
9. Anais Brasileiros de Dermatologia ^b	PMC	Sociedade Brasileira de Dermatologia
10. APSP Journal of Case Reports	PMC	EL-MED Publishers Pakistan
11. BMJ Case Reports ^b	MEDLINE, Scopus	BMJ Publishing Group
12. Case Reports in Anesthesiology	PMC	Hindawi
13. Case Reports in Cardiology	PMC	Hindawi
14. Case Reports in Critical Care	PMC	Hindawi
15. Case Reports in Dermatological Medicine	PMC	Hindawi
16. Case Reports in Dermatology	PMC	Karger
17. Case Reports in Emergency Medicine	PMC	Hindawi
18. Case Reports in Endocrinology	PMC	Hindawi
19. Case Reports in Gastroenterology	PMC	Karger
20. Case Reports in Gastrointestinal Medicine	PMC	Hindawi
21. Case Reports in Genetics	PMC	Hindawi
22. Case Reports in Hematology	PMC	Hindawi
23. Case Reports in Hepatology	PMC	Hindawi
24. Case Reports in Immunology	PMC	Hindawi
25. Case Reports in Infectious Diseases	PMC	Hindawi
26. Case Reports in Medicine	PMC	Hindawi
27. Case Reports in Nephrology	PMC	Hindawi
28. Case Reports in Nephrology and Dialysis	PMC	Karger
29. Case Reports in Neurological Medicine	PMC	Hindawi
30. Case Reports in Neurology	PMC	Karger
31. Case Reports in Obstetrics and Gynecology	PMC	Hindawi
32. Case Reports in Oncological Medicine	PMC	Hindawi
33. Case Reports in Oncology	PMC	Karger
34. Case Reports in Ophthalmological Medicine	PMC	Hindawi
35. Case Reports in Ophthalmology	PMC	Karger
36. Case Reports in Orthopedics	PMC	Hindawi
37. Case Reports in Otolaryngology	PMC	Hindawi
38. Case Reports in Pathology	PMC	Hindawi
39. Case Reports in Pediatrics	PMC	Hindawi
40. Case Reports in Psychiatry	PMC	Hindawi
41. Case Reports in Pulmonology	PMC	Hindawi
42. Case Reports in Radiology	PMC	Hindawi
43. Case Reports in Rheumatology	PMC	Hindawi
44. Case Reports in Surgery	PMC	Hindawi
45. Case Reports in Transplantation	PMC	Hindawi
46. Case Reports in Urology	PMC	Hindawi
47. Case Reports in Vascular Medicine	PMC	Hindawi
48. Case Reports in Women's Health	Scopus	Elsevier
49. CEN (Clinical and Experimental Nephrology) Case Reports	PMC	Springer
50. Cephalalgia ^b	IF, Scopus	Sage
51. Clinical Case Reports	PMC	Wiley
52. Clinical Cases in Mineral and Bone Metabolism	PMC	CIC Edizioni Internazionali
53. Columbian Journal of Anesthesiology ^b	Hinari	Elsevier
54. Case Reports in Plastic surgery and Hand surgery	PMC	Taylor and Francis
55. Deutsche Ärzteblatt ^b	MEDLINE, Scopus	German Medical Association
56. Endocrinology, Diabetes and Metabolism Case Reports	PMC	Bioscientifica Ltd.
57. Epilepsy and Behavior Case Reports	PMC, Scopus	Elsevier
58. European Journal of Case Reports in Internal Medicine	MEDLINE, Scopus	SMC media Sri
59. European Journal of Pediatric Surgery Reports	PMC	Thieme
60. Explore—The Journal of Science and Healing ^b	IF, MEDLINE, Scopus	Elsevier
61. Global Advances in Health and Medicine ^b	PMC, Hinari	Sage
62. Gynecologic Oncology Case Reports	PMC, Scopus	Elsevier

(Continued)

Table 1. Continued

Journal title ^a	Indexed	Publisher
63. Headache ^b	IF, MEDLINE, Scopus	Wiley
64. HeartRhythm Case Reports	Scopus	Elsevier
65. Human Pathology: Case Reports	Scopus	Elsevier
66. Integrative Medicine: A Clinician's Journal ^b	PMC	Innovision Health Media
67. International Journal of Surgery Case Reports	PMC, Scopus	Elsevier
68. International Medical Case Reports Journal	PMC	Dove Medical Press
69. JAAD Case Reports (Dermatology)	Scopus	Elsevier
70. Journal of Clinical Epidemiology ^b	IF, MEDLINE, Scopus	Elsevier
71. Journal of Dermatological Case Reports	PMC	Poland - Spejaliści Dermatologii
72. Journal of Dietary Supplements ^b	MEDLINE, Scopus	Taylor and Francis
73. Journal of Endourology Case Reports	PMC	Mary Ann Liebert
74. Journal of Investigative Med. High Impact Case Reports	PMC	Sage
75. Journal of Medical Case Reports ^b	MEDLINE, PMC, Scopus	Biomed Central
76. Journal of Neurological Surgery Reports	PMC	Thieme
77. Journal of Orthopedic Case Reports	PMC	Indian Orthopedic Research Group
78. Journal of Pediatric Surgery Case Reports	Scopus	Elsevier
79. Journal of Radiology Case Reports	PMC	EduRad Publishing
80. Journal of Surgical Case Reports	PMC	Oxford
81. Medical Mycology Case Reports	PMC, Scopus	Elsevier
82. Neurocase	IF, MEDLINE, Scopus	Taylor and Francis
83. Neurology: Clinical Practice	PMC, Scopus	American Academy of Neurology
84. Oxford Medical Case Reports	PMC	Oxford University Press
85. Radiology Case Reports	Scopus	Elsevier
86. Rare Tumors	PMC	Page Press
87. Respiratory Medicine Case Reports	PMC, Scopus	Elsevier
88. Retinal Cases and Brief Reports	MEDLINE, Scopus	Wolters Kluwer Health
89. SAGE Open Medical Case Reports	PMC	Sage
90. The Permanente Journal ^{b,c}	MEDLINE, PMC, Scopus	The Permanente Press
91. Thoracic and Cardiovascular Surgeon Reports	PMC	Thieme

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; IF, impact factor (Journal Citation Reports); Med., medicine; PMC, PubMed Central.

^a Other medical journals may publish case reports within articles.

^b Endorsed Care Guidelines.

^c Open access, no article processing charge (APC).

2.3. Item 2. Keywords section

CARE Checklist description: the key elements of this case are in 2–5 words.

2.3.1. Explanation

Medical journals sometimes require authors to choose keywords for case reports. Keywords that identify the focus of the case report can be selected using MeSH terminology (available at www.pubmed.com) or Google Scholar. Include the word “case report” as one of the keywords to identify the type of publication and aid database searches.

2.3.2. Example

- Impending aortic aneurysm rupture—a case report and review of the warning signs [17].

Keywords: “abdominal aortic aneurysm; aorta; case report; hyperattenuating crescent; imaging; mural thrombus; review; rupture”

2.4. Item 3. Abstract section

2.4.1. CARE Checklist description

3a Introduction—What does this case add?

3b Case presentation:

- The main symptoms of the patient(s).
- The main clinical findings.
- The main diagnoses and interventions.
- The main outcomes.

3c Conclusion—What are the main “take-away” lessons from this case?

2.4.2. Explanation

The abstract is often the first section a reader encounters, providing a summary to help them determine their interest in the case report [18,19]. Abstracts provide a balanced and succinct summary of the full report and customarily range from 100 to 250 words, depending on the journal [20]. The abstract also aids indexing and identification of case reports in electronic databases [21].

The case report's abstract first briefly summarizes the background information in a sentence or two to orient the reader to the relationship between existing knowledge

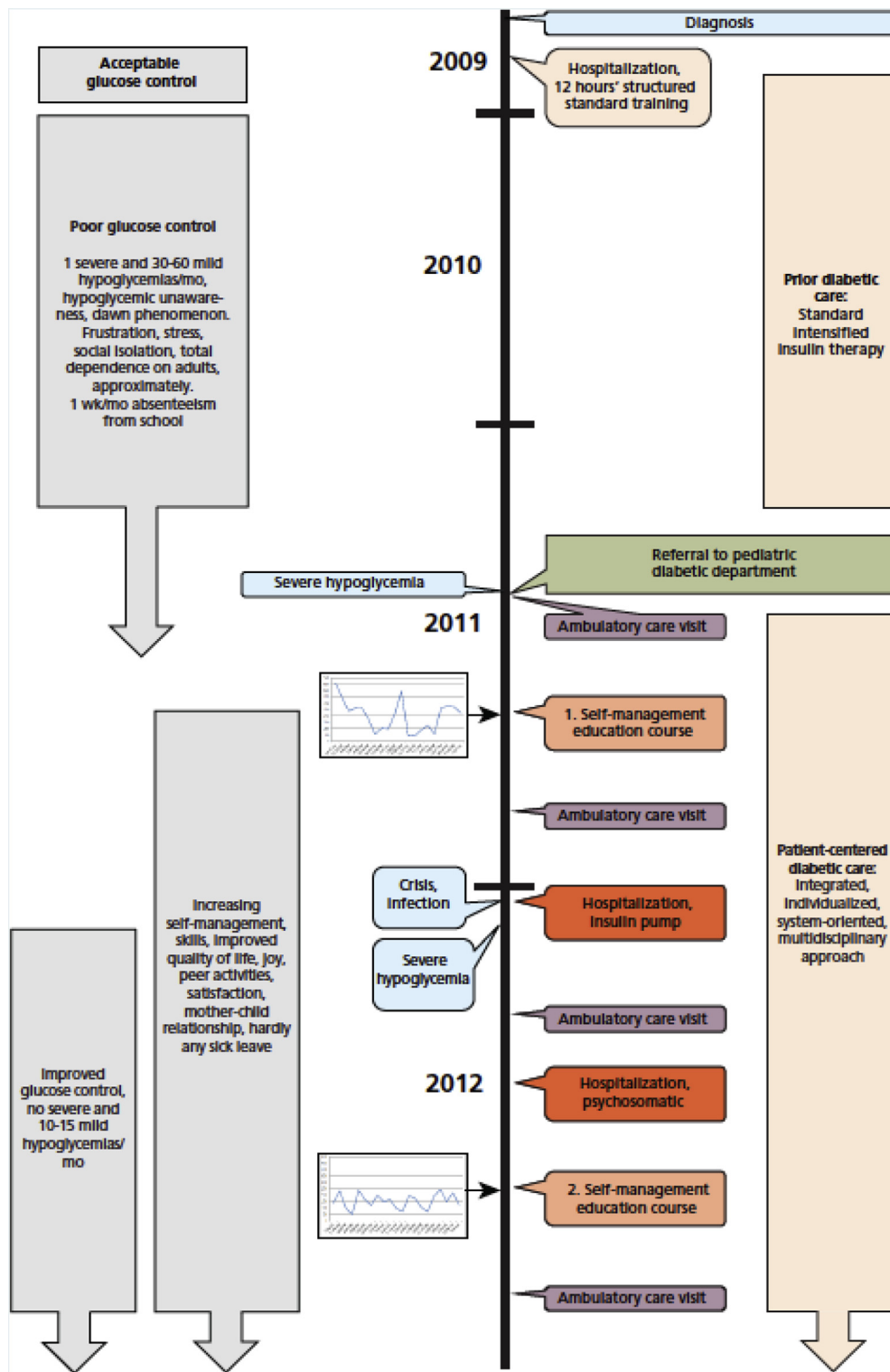


Fig. 1. Timeline of interventions and outcomes. Patient-centered diabetes care in children: an integrated, individualized, systems-oriented, and multidisciplinary approach [14].

and the case. Second, the case report identifies the focus of the case report and summarizes this episode of care. Finally, the abstract concludes with one to two sentences that highlight the “take-away” lesson from the case

report, with an emphasis on a single priority message [22,23].

When written last, the abstract can often more accurately reflect the completed case report. Medical journals

vary in their requirements for an unstructured versus a structured abstract. A structured abstract for a case report typically includes three sections: the introduction, case presentation, and conclusion [18,20].

2.4.3. Two examples

2.4.3.1. Unstructured

- Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS) [24].

“A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumor virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies, it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.”

2.4.3.2. Structured

- Association between isotretinoin use and central retinal vein occlusion in an adolescent with minor predisposition for thrombotic incidents: a case report [25].

“Introduction: We report an adolescent boy with minimal pre-existing risk for thromboses who suffered central retinal vein occlusion associated with isotretinoin use for acne. To the best of our knowledge, this is the first well-documented case of this association.

Case presentation: An otherwise healthy 17-year-old white man who was treated with systemic isotretinoin for recalcitrant acne was referred with central retinal vein occlusion in one eye. Although a detailed investigation was negative, DNA testing revealed that the patient was a heterozygous carrier of the G20210A mutation of the prothrombin gene. Despite the fact that this particular mutation is thought to represent only a minor risk factor for thromboses, it is probable that isotretinoin treatment greatly increased the risk of a vaso-occlusive incident in this patient.

Conclusion: Isotretinoin use may be associated with sight- and life-threatening thrombotic adverse effects even in young patients with otherwise minimal thrombophilic risk. Physicians should be aware of such potential dangers.”

2.5. Item 4. Introduction section

CARE Checklist description: Brief background summary of the case referencing the relevant medical literature.

2.5.1. Explanation

The introduction provides context for the case report related to the patient’s episode of care and may elaborate a demonstration of need. The most important studies may be cited to introduce readers to the topic; however, a detailed discussion of relevant studies—such as a comprehensive literature review accompanying the case report—is best left to the discussion section [19,26,27]. We recommend that case reports following the CARE Guidelines should include the following statement: “This case report was prepared following the CARE Guidelines” and include a citation of the CARE Statement publication. Referencing the guidelines informs the reader of the standards for reporting and facilitates the evaluation of the adherence to the guidelines [28]. The introduction generally ends with a 1–3 sentence synopsis of the case that identifies a question and/or gap in knowledge, the importance of this patient case, and a single priority message [20].

2.5.2. Examples

- Extensive deep vein thrombosis following prolonged gaming (“gamer’s thrombosis”): a case report [29].

“A period of prolonged seated immobility is recognized as one of the major risk factors for developing venous thrombosis. Long-distance air travel and prolonged sitting in relation to work or recreation have been shown to increase the risk of venous thrombosis [1,2]. A recent survey has found that the average time spent playing video games is increasing and that gamers in the United States spend an average of 13 hours each week playing computer games [3]. Prolonged immobility associated with gaming may therefore be an important risk factor for venous thromboembolism. We report a case of a 31-year-old man who developed extensive deep vein thrombosis associated with prolonged playing of PlayStation games.”

- PCP and mucosal candidiasis in previously healthy homosexual men; evidence of a new acquired cellular immunodeficiency [30].

“Acquired T-cell defects are well known to occur in adults with untreated Hodgkin’s disease, sarcoidosis, and viral infections. These noniatrogenic T-cell deficiencies are marked by cutaneous anergy and diminished proliferative responses to mitogens and antigens in vitro. Opportunistic infections rarely occur in the absence of immunosuppressive therapy. We recently treated several young, previously healthy, homosexual men for multiple episodes of *P. carinii* pneumonia, extensive mucosal candidiasis, and severe viral infections. The clinical manifestations and studies of cellular immune function

Table 2. Patient identifiers**Patient identifiers to be excluded in the United States**

<http://www.hhs.gov/sites/default/files/hipaa-simplification-201303.pdf>

- Names
- Geographic regions
- Elements of dates including birth date, date of death, and admission/discharge date
- Listing ages older than 89 years require additional consent unless providing a single category of age >90 years
- Telephone numbers, fax numbers, and e-mail addresses
- Personal identifying numbers (e.g., social security numbers, medical record numbers)
- Web Universal Resource Locators (URLs) and Internet Protocol (IP) addresses
- Biometric identifiers, photographs and images (without specific additional permission [31],
- Other unique, identifying characteristics or codes

in these patients indicated a similar severe acquired T-cell defect. Several lines of evidence suggested that cytomegalovirus infection was a major factor in the pathogenesis of the immunocompromised state. This syndrome represents a potentially transmissible immune deficiency.”

2.6. Item 5. Patient information section

CARE Checklist description:

- 5a Demographic information of the patient (age, gender, ethnicity, occupation).
- 5b Main symptoms of the patient (chief complaint).
- 5c Medical, family, and psychosocial history—including lifestyle and genetic information whenever possible, details about relevant comorbidities, and past interventions, and their outcomes.

2.6.1. Explanation

We suggest including relevant demographic information about the patient while maintaining anonymity. Characteristics to identify the patient should ideally include age, sex and gender, race, and ethnicity—these characteristics may become important if many cases are subsequently reported. See [Table 2](#), from the US Department of Health and Human Services, of some personal identifiers that should not be used in a case report because they might reveal the patient’s identity.

When appropriate, include the patient’s own words about their chief complaint or symptoms that led to their initial visit. Specify how long symptoms have been present and if relevant, the frequency, intensity, location, and aggravating or alleviating factors. Distinguish comorbidities, when they began, whether they are recurring, past and current interventions and their outcomes. When discussing a history of allergies, include allergens, dates of reactions, and the type of allergic manifestation [20].

Other historical factors may be relevant, such as:

- Perinatal history, such as type of birth, length of pregnancy, if breast-fed, and for how long
- Psychosocial history (e.g., occupation, social support, education level)
- Type of health insurance
- Environmental exposures (living and working environment, potential toxic exposures)
- Lifestyle (sleep, stress management, exercise, recreational drug use, smoking, alcohol consumption, and nutrition/diet)
- Family medical history (e.g., if family members have similar conditions as the patient)
- Genetic information (relevant to the case)

2.6.2. Examples

5a, 5b, and 5c—Patient information.

- Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C [32].

“Case Report: The proband is a male born in 1942. At the age of 19 years, he had his first episode of deep venous thrombosis in one leg. After this, he was healthy and free of thrombosis for almost 20 years. Between 1980 and 1987, he had multiple episodes of deep venous thrombosis, at least once a year. The thrombotic events were treated with vitamin K antagonists for periods of up to 3 months. The presence of a thrombus was verified with phlebography on at least two occasions. The proband has developed a postthrombotic syndrome in his legs but has no other disorders. Several members of the proband’s family have similar histories of multiple episodes of deep venous thrombosis ([Fig. 1](#)). His older brother by 10 years (III-2) has had deep venous thrombosis (in the legs) on several occasions, most of them occurring between the ages of 45 and 50 years. Also, his uncle (II-7) and aunt (II-5) have both had multiple episodes of thrombosis.

A younger relative (IV-2) had clinically suspected deep venous thrombosis during her third pregnancy, but phlebography failed technically. The proband’s father, who had no history of thrombosis, is deceased. Nineteen of the family members (all living members of generations II–IV) were available for testing. Two additional, unrelated cases with thrombophilia and inherited poor response to APC were identified; their medical histories are briefly described in the legend to [Fig. 6](#).”

- Quinacrine-induced cholestatic hepatitis in undifferentiated connective tissue disease (UCTD) [33].

“A 45-year-old African-American woman presented to the rheumatology clinic with a history of UCTD, manifesting as biopsy-proven urticarial dermatitis, inflammatory arthritis, fatigue, and weight loss in the setting of positive immunofluorescence antinuclear antibodies (1:160, speckled pattern), anti-RNP, anti-Sm/RNP, and antichromatin antibodies.”

2.7. Item 6. Clinical findings section

CARE Checklist description: Describe the relevant physical examination (PE) findings.

2.7.1. Explanation

Report relevant data from the PE and other significant clinical findings identified at the onset of care in the clinical findings section, along with an explanation of the examination methods, if necessary. These can be listed in the text and may include deidentified photographs. In some subspecialties, the notation used to describe the physical examination (e.g., ophthalmology) is unique, and the description of the examination may require additional explanation. If the physical findings are extensive, they may be organized as a summary table or figure. Record relevant findings that occurred during the course of care, with dates, in the “Follow-Up and Outcomes” section.

2.7.2. Example

- Mycobacterium tuberculosis monoarthritis in a child [34].

“At age 2 years 10 months, this previously healthy North American Indian girl presented with a 3-week history of left knee swelling and morning stiffness without associated symptoms. There were no infectious contacts reported at the first presentation. On the initial physical examination, the left knee was moderately swollen and warm with signs of both intra-articular fluid and synovial hypertrophy. Flexion and extension were limited by 10°. The child was afebrile and appeared otherwise healthy. There were no abnormal pulmonary signs and no peripheral lymphadenopathy. The remainder of the examination was normal.”

2.8. Item 7. Timeline section

CARE Checklist description: Depict important date and times in this case (table or figure)

2.8.1. Explanation

A timeline presents relevant events in the patient’s history in chronological order in a figure or table and offers a succinct summary of one or more key events in the case, enabling the reader to readily view core elements of the case report. These core elements might include the following: a brief patient and family medical history; chief complaints; factors related to susceptibility; diagnostic evaluations; therapeutic interventions; care received from other clinicians; follow-up; and outcomes. In some cases, pictures may be incorporated into the timeline.

2.8.2. Examples

- Plasma resistant atypical hemolytic uremic syndrome associated with a CFH mutation treated with eculizumab: a case report [35].

- Patient-centered diabetes care in children: an integrated, individualized, systems-oriented, and multidisciplinary approach [16].

2.9. Item 8. Diagnostic assessment and diagnosis section

CARE Checklist description:

- 8a Diagnostic methods (e.g., physical examination, laboratory testing, imaging, questionnaires)
- 8b Diagnostic challenges (e.g., financial, language, or cultural)
- 8c Diagnostic reasoning including other diagnoses considered
- 8d Prognostic characteristics (e.g., staging) where applicable

2.9.1. Explanation

Most case reports describe patients whose presentation is either a rare manifestation of an established disease or the first clue to a previously unknown disease. In either case, an accurate diagnosis is the essential element of a case report, and the author must provide a complete description of the diagnostic process. Whether a patient whose presentation is a rare manifestation of an established disease or the first clue to a previously unknown disease, the diagnostic assessments are essential. We recommend reporting relevant deidentified results of diagnostic evaluations with the dates they were performed. These could include laboratory results, radiographic and cardiographic images, and patient-reported outcome measurement surveys [36]. Include a brief explanation of the relevant results with reference ranges if necessary [20]. When trying to establish a cause and effect relationship between an exposure and a clinical event, document time course and dose of exposure to the onset of the clinical syndrome [37]. Important follow-up diagnostic assessments should be reported in the “Follow-up and Outcomes” section.

A case report should, if possible, cite literature references that support or challenge the main diagnostic hypotheses. Other diagnostic challenges such as obstacles to completing the evaluation may be important to mention. Likewise, discuss the evidence for the prognosis which may be affected by factors such as histological and genetic abnormalities, concomitant diagnoses, and therapeutic interventions used. These can be further elaborated in the discussion section.

2.9.2. Examples

2.9.2.1. 8a—Diagnostic methods (e.g., PE, laboratory testing, imaging, questionnaires)

- Branch facial nerve trauma after superficial temporal artery biopsy: a case report [38].

“Investigations were significant for a magnetic resonance imaging (MRI) study with and without contrast that revealed cerebral ischemic gliosis compatible with the patient’s age without acute intracranial pathology. There were no abnormalities noted along the course of either cranial seventh nerve. Her left STAB incision did not show evidence of thrombus, inflammation, or giant cells and hence was without evidence of temporal arteritis.”

2.9.2.2. 8b—Diagnostic challenges (e.g., financial, language, or cultural)

- Chiari malformation type I with cervicothoracic syringomyelia masquerading as bibrachial amyotrophy: a case report [39].

“Delay of diagnosis resulted in a severe gradual deterioration in our patient. His initial clinical diagnosis of muscular dystrophy was further confirmed with diagnostic studies, according to the family, although we acknowledge that another muscle biopsy may be needed to exclude a diagnosis of muscular dystrophy (though we doubt that this was the actual diagnosis). As a result of the original diagnosis, however, our patient did not seek further evaluation for several years because he understood that there was no treatment for his condition. Decades later, further work-up with simple imaging techniques easily confirmed the etiology of his symptoms. Unfortunately, this delay in diagnosis resulted in the development of irreversible severe chronic muscle wasting. With such advanced atrophy and severe weakness, surgery will likely not provide significant functional benefit.

The differential diagnosis of bibrachial atrophy and syringomyelia is important. While we cannot definitively exclude that both the cervicothoracic syringomyelia and the bibrachial amyotrophy occurred as two separate entities, we doubt this.... We do not know why our patient’s symptoms were stable for over 20 years. Although there was no history of any preceding head or neck trauma, perhaps the syrinx rapidly enlarged in the process of the disease. Without prior imaging, this is impossible to say with any certainty.”

2.9.2.3. 8c—Diagnostic reasoning including other diagnoses considered

- Severe liver involvement in two patients with long-term history of fever: remember familial Mediterranean fever [40].

“Differential diagnosis.

Taking carefully into account the previous in-depth history of both patients, a molecular analysis of the MEFV gene was decided. A rapid screening test of the entire coding sequence of MEFV gene, combined with targeted sequencing, revealed that both patients suffered from FMF as no other etiology had been identified thus far, whereas there was an appropriate exclusion of infectious,

malignant, autoimmune, rheumatic, and liver and biliary diseases at their last submission. Actually, the mutational analysis revealed that the male patient carried the R202Q/R202Q homozygous alteration in exon 2 of the MEFV gene, whereas the female young patient was heterozygous for the M694V/0 conservative mutation in exon 10 and homozygous for the R202Q/R202Q mutation in exon 2.”

2.9.2.4. 8d—Prognostic characteristics (e.g., staging) where applicable

- Procalcitonin as a diagnostic and prognostic marker for sepsis caused by intestinal infection: a case report [41].

“Procalcitonin is a useful tool in the early diagnosis of sepsis, differentiating from other inflammatory syndrome. The high PCT level (10 ng/mL) in this case could suggest serious bacterial infection and sepsis and also predicts mortality and worse outcome.”

2.10. Item 9. Therapeutic interventions section

CARE Checklist description:

- 9a Types of intervention (e.g., pharmacologic, surgical, preventive, self-care)
- 9b Administration (e.g., dosage, strength, duration)
- 9c Changes in intervention (with rationale)

2.10.1. Explanation

Therapeutic interventions are often the focus of case reports or they may provide key diagnostic information. In either case, we recommend reporting them in enough detail to facilitate replication. Complex or poorly defined interventions may benefit from use of the TIDieR guideline (a CONSORT extension) to enhance the accuracy, transparency, and reproducibility of an intervention [42].

Table 3. Therapeutic intervention descriptions

All interventions
<ul style="list-style-type: none"> • Specify type of intervention, indicated condition, and intervention [42]
Pharmaceuticals (over-the-counter and prescription drugs)
<ul style="list-style-type: none"> • International nonproprietary name (INN), dosing regimen, and length of intervention • For formulations that are administered as volumes of a fluid (e.g., intravenous infusions or oral liquid formulations) state the concentration of the formulation • Provide manufacturer and brand names if relevant
Dietary supplements and botanical medicines
<ul style="list-style-type: none"> • Ingredients and dosing regimen (e.g., EPA [eicosapentaenoic acid] 750 mg plus DHA [docosahexaenoic acid] 250 mg, 1 capsule orally once daily for 6 months) • If medicinal plants are used, indicate plant species using the Latin binomial name, the quantity of herbal substance or constituents, and the parts of the plant • Provide manufacturer and brand names if relevant
Lifestyle recommendations (e.g., physical activity or exercise)
<ul style="list-style-type: none"> • Frequency, intensity, timing, and type

A brief explanation of why the patient received a particular intervention (such as the target condition, the preexposure clinical course, etc.) should be provided in this section; however, we suggest reserving a more detailed rationale for the discussion section. The general format for reporting interventions is outlined below (see Table 3). Case reports focusing on harms should include the manufacturer and brand of the products in question. Explain changes made to an intervention and describe care received from other providers.

2.10.2. Examples

2.10.2.1. 9a—Types of intervention (e.g., pharmacologic, surgical, preventive, self-care)

- Eight years of follow-up after laminectomy of calcium pyrophosphate crystal deposition in the cervical yellow ligament of patient with Coffin–Lowry syndrome: a case report [43].

“Surgery

Under general anesthesia in the prone position, the C1–C7 laminae were exposed. Twenty millimeters of the width of the C2–C7 laminae were removed using a high-speed drill. Adhesions between the calcification and dura mater were gently stripped off, and the laminae were resected en block with the calcification. Fifteen millimeters of the width of the C1 posterior arch was removed using a high-speed drill. Pulsating dura mater was observed after laminectomy, but the pulse was weak. The dura mater appeared hypertrophic; however, we did not incise the dura mater.”

2.10.2.2. 9b—Administration (e.g., dosage, strength, duration)

- Maintenance eculizumab dose adjustment in the treatment of atypical hemolytic uremic syndrome: a case report and review of the literature [44].

“The patient was started on induction eculizumab at 900 mg IV weekly for 4 weeks and responded well with improvement in platelet count and renal function. He was transitioned to every-other-week maintenance eculizumab, and hemodialysis was discontinued.”

- Polysubstance-induced relapse of schizoaffective disorder refractory to high-dose antipsychotic medications: a case report [45].

“Rapid sedation was commenced with ziprasidone, lorazepam, droperidol, and zuclopenthixol acetate (Table 4). Benzotropine was administered for prophylaxis against extrapyramidal side effects of the antipsychotic medications. The level of sedation attained was unsatisfactory as he remained severely agitated and combative interspersed with only brief periods of drowsiness. He could not follow direction or adhere to boundaries established by staff. All attempts at de-escalation and distraction were met with aggression.

Example 9B—Table from example.

2.10.2.3. 9c—Changes in intervention (with rationale)

- Severe refractory autoimmune hemolytic anemia with both warm and cold autoantibodies that responded completely to a single cycle of rituximab: a case report [46].

“Partial resolution of the hemolytic process was observed while the patient was treated with daily plasmapheresis with 5% albumin, at a volume of 3L–4L. A total of seven daily plasmapheresis treatments were performed, which resulted in a gradual decrease of the patient’s LDH and bilirubin and a rise in his level of haptoglobin. However, the patient still required almost daily blood transfusions. On the basis of earlier reports indicating an anecdotal benefit of rituximab treatment for immune cytopenias, plasmapheresis was discontinued and our patient was placed on rituximab therapy at a dose of 375 mg/m² every week. A total of four doses were administered over a period of 4 weeks. Although an initial increase in LDH level after the initiation of rituximab treatment was noted, there was no evidence of worsening hemolysis. After the first two courses of rituximab therapy, the patient showed a marked clinical improvement. His hemoglobin level stabilized... and he no longer required blood transfusions.”

Table 4. Medications administered to the patient in our emergency department and selected behavioral observations

Time	Medication name, dose, and route	Behavioral observations
17:20	Approximate time of presentation to our emergency department	Extremely aggressive, threatening, and offensive behavior and language
17:26	Ziprasidone 20 mg IM, lorazepam 2 mg IM	
17:30	Lorazepam 2 mg IM	
17:40	Zuclopenthixol acetate 150 mg IM, benzotropine 2 mg IM	
18:05	Lorazepam 2 mg IV	Vital signs and IV access obtained, blood sampled
18:30	Droperidol 10 mg IM	Verbally abusive, threatening, aggressive
22:30	Ziprasidone 20 mg IM	
23:00	Lorazepam 2 mg IV	
01:00		Sedated and quiet
04:00	Droperidol 10 mg IM, Lorazepam 2 mg IV	Yelling, abusive, shaking bed, threatening staff
06:00		Sedated but intermittent abuse and threats
11:20	Ziprasidone 20 mg IM	
13:00	Droperidol 25 mg IM	Acute arousal, combative during transport to psychiatric ward”

2.11. Item 10. Follow-up and outcomes section

CARE Checklist description:

- 10a Clinician and patient-assessed outcomes
- 10b Important follow-up test results (positive and negative)
- 10c Intervention adherence and tolerability (and how this was assessed)
- 10d Adverse and unanticipated events

2.11.1. Explanation

We recommend reporting objective and subjective findings throughout the course of care, to track changes in the outcomes of interest. Clinician-assessed outcomes could include objective outcome measures, such as laboratory biomarkers, physical findings, and imaging. Longitudinal clinical findings may help to create a convincing case and support the discussion of temporal or other relationships between outcomes and treatment, a topic to be explored further in the discussion section [20,27].

Reporting results from longitudinal data including patient-assessed and clinician-assessed outcomes may strengthen the case for a causal link. We suggest reporting other clinical management received by the patient, along with its potential impact on outcomes. Consulting with other providers and including their perspective may be helpful.

If the intervention is a focus of the case report, include patient adherence to that intervention and how this information was obtained (e.g., diary/log, telephone call, electronic methods). If available, describe harms attributed to an

intervention and make note of the patient's words, reporting what the adverse outcomes were, how often they occurred, and with what intensity [22]. All case reports should explicitly mention the presence or absence of adverse events.

2.11.2. Examples

2.11.2.1. 10a—Clinician and patient-assessed outcomes

- Self-directed mindfulness training and improvement in blood pressure, migraine frequency, and quality of life [47].

“The results of 8 weeks of self-directed mindfulness training plus 3 additional weeks of customized mindfulness practice resulted in both personally and clinically meaningful outcomes.

From the patient's perspective, perceived stress was dramatically reduced. Not only was MR calmer about her previously overwhelming workload but her workload actually decreased because of increases in her efficiency and focus. For example, her e-mail inbox, a source of perpetual stress, came under control... Using MBSR focusing techniques, she turned email into tasks that were immediately accomplished and the email inbox was successfully reduced to very few items and is now emptied several times a day.

Clinically important objective measures of disease risk also improved during her mindfulness meditation experience. MR measured and recorded her blood pressure using an automated blood pressure monitor (Omron model HEM-609, Lake Forest, IL) immediately before and after her

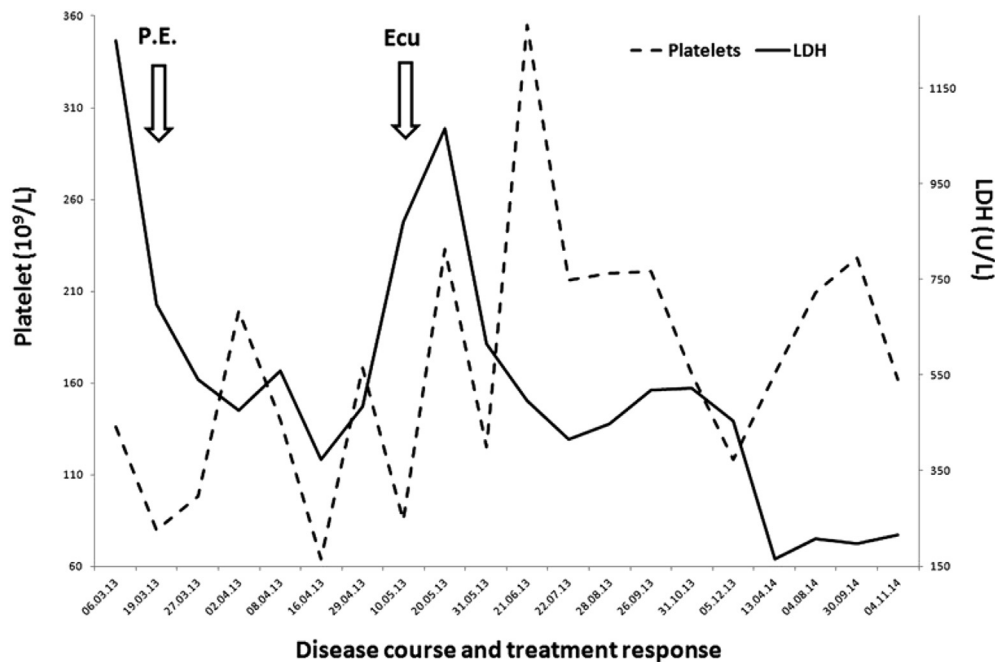


Fig. 2. Disease course and treatment response. The timeline from presentation detailing platelet and lactate dehydrogenase (LDH) response to plasma exchange and eculizumab (Ecu). Plasma-resistant atypical hemolytic uremic syndrome associated with a complement factor H mutation treated with eculizumab: a case report [35].

meditation sessions. In the first 8 weeks of mindfulness training, baseline blood pressure was typically elevated and classifiable as stage I hypertension. Following 45 minutes of meditation, blood pressure was reduced into the prehypertensive range and into the normal range after 10 weeks of practice. The maximal mean reduction in both systolic and diastolic blood pressure occurred after approximately 4 weeks (−18.5 mm Hg systolic and −25.8 mm Hg diastolic). By week 7, both systolic and diastolic blood pressure had come within the prehypertensive range and continued to decline to optimal levels (Fig. 1). At the end of the 8-week program and an additional 3 weeks of continued self-directed practice and data recording, pre-meditation mean systolic and diastolic blood pressures were significantly reduced. When all daily blood pressure observations were combined, the mean reductions were highly significant: $P < .0001$ for systolic and $P < .0004$ for diastolic blood pressure reductions over the 11-week period (Fig. 2). Notably, as blood pressure came within the normal range, the difference before and after meditation also decreased, suggesting MR was maintaining a lower sympathetic tone.

The additional symptoms and behaviors she tracked, such as migraines and exercise, also were reviewed. Migraine frequency was decreased, and through MRs mindful attention to her inner experience, it was determined that migraines were now occurring only in conjunction with the phase of her menstrual cycle. Knowledge of this enabled her to plan accordingly and use her migraine abortive medications appropriately. Body weight, which has been a long-term struggle, has not changed in the 11 weeks of mindfulness meditation. MR has taken the ‘attitudes and commitment’ portion of her 8-week MBSR training very seriously.”

2.11.2.2. 10b—Important follow-up test results (positive and negative)

- Acute cerebellitis successfully managed with temporary cerebrospinal fluid diversion using a long tunnel external ventricular drain [EVD]: a long-term radiological follow-up of two cases [48].

“Outcome and follow-up [Case 1]

The child was extubated on day 3, but the EVD was retained and kept at 10 cm H₂O. It was removed after challenge on day 9. A repeat MRI showed markedly decreased cerebellar edema. The child regained a Glasgow Coma Scale score of 15/15 and was discharged on the 11th day of admission, with no neurological deficits. He remained asymptomatic at 2-year follow-up, at which time an MRI was also found to be normal.”

“Outcome and follow-up [Case 2]

The infant’s condition gradually improved, and he started tolerating breast feed. The EVD was removed after 10 days, and a repeat MRI with and without contrast, and MR venogram, showed no venous involvement and

resolution of all pathological findings, including the cerebellar swelling, tonsillar herniation, and hydrocephalus. The patient was discharged on oral dexamethasone tapered over several weeks. At 1-year follow-up, the patient showed no neurological deficits and displayed normal growth and development.”

2.11.2.3. 10c—Intervention adherence and tolerability (and how this was assessed)

- Quetiapine-induced sleep-related eating disorder like behavior: a case series [49].

“Our patients had a few important predisposing factors for parasomnia including increased work-related stress, depression, and severe sleep apnea with high arousal index. If a patient with parasomnia has any other concomitant primary sleep disorder, the treatment is initially directed toward that aspect which often resolves the parasomnia. Our first patient had severe sleep apnea that was treated adequately, but he continued to have sleepwalking and SRED despite good compliance with treatment probably because his SWS had increased after using BiPAP. Our second patient was not able to be compliant with the CPAP initially until she stopped taking quetiapine.”

2.11.2.4. 10d—Adverse and unanticipated events

- Altered distribution of digoxin in renal failure—a cause of digoxin toxicity? [50]?

“A 56-year-old man weighing 77 kg was admitted with an acute anterior myocardial infarct having had a previous myocardial infarct 2 years before. He had pulmonary edema due to left ventricular failure which partly responded to treatment with furosemide and diamorphine, and he had occasional ventricular extra systoles which were controlled with small doses of lignocaine. On admission, he was in mild renal failure, and over the next 36 hours, this deteriorated to the point where his plasma urea was 125 mg% and creatinine 2.03 mg%. At that time, he was given a total of 1 mg of digoxin orally (13 µg/kg) in three divided doses and shortly after the third developed the various arrhythmias which are shown in Fig. 2; just before a further dose of 0.25 mg intramuscularly; however, he had reverted to sinus rhythm and following that dose he once more developed various arrhythmias. Treatment at different times with intravenous procainamide and intravenous and oral practolol did not affect his arrhythmias, and he had already reverted to sinus rhythm when only one dose of diphenylhydantoin (50 mg) had been given orally. Other drugs which he received were heparin, warfarin, ampicillin, potassium chloride, and diazepam. His plasma digoxin levels following the fourth dose of digoxin are shown in Fig. 2. Only when the plasma digoxin level fell below 1.7 ng/mL was he free from arrhythmias. His T_{1/2β} was

37.9 h and his V_d 264 L (32.4 L/kg). At a later date, when his renal function had improved slightly (urea 47 mg%, creatinine 1.37 mg%, creatinine clearance 41 ml/min), his steady-state plasma level on a reintroduced daily maintenance dose of 0.125 mg orally was 0.5 ng/mL indicating a V_d of 349 L (4.5 L/kg).”

2.12. 11. Discussion (including conclusion) section

CARE Checklist: Discussion (including conclusion):

- 11a Strengths and limitations of the management of this case
- 11b Relevant medical literature
- 11c Rationale for conclusions (including assessment of cause and effect)
- 11d Main “take-away” lessons of this case report

2.12.1. Explanation

Case reports may offer new perspectives on new or rare diseases, unusual disease presentations, therapeutic interventions, or harms [51]. Succinctly discuss the key features of the case and what was learned. Basic mechanisms or principles (e.g., pathophysiological, immunological, social) and diagnostic challenges may be important, particularly if they help explain observations. Compare the results in the case with results from clinical trials and case reports [18,22]. Support recommendations for additional research with published references. It is important to transparently discuss limitations, including mentioning that the results from a single case may not be applicable to patients in general [18].

The conclusion section is often brief and focuses on the primary lessons learned from the case report.

2.12.2. Examples

2.12.2.1. 11a—Strengths and limitations of the management of this case

- Altered distribution of digoxin in renal failure—a case of digoxin toxicity? [50]

“The data which we have presented here have been limited by the restrictions of clinical practice, and in the appendix, we have outlined the major shortcomings of the pharmacokinetic calculations we have made. However, despite the difficulties in deriving accurate estimates of the true apparent volumes of distribution involved, the changes we have observed are too large merely to be accounted for by pharmacokinetic inaccuracies; indeed, any overestimation of the true volumes strengthens the argument. We believe that the changes we have observed are real and have contributed to the digoxin toxicity which occurred in these patients. Further characterization of the cause of the abnormal distribution of digoxin in renal failure by more precise prospective clinical studies is required.”

2.12.2.2. 11b—Relevant medical literature

- Successful heart transplantation after 13 hours of donor heart ischemia with the use of HTK solution: a case report [16].

“Dr Barnard successfully used a hypothermic perfusion system to protect a donor heart for more than 16 hours in heterotopic HTx [52]. However, surgeons are more conservative while performing orthotopic HTx. Few series are using donor hearts with IT longer than 6 hours. Long-term follow-up of HTx recipients at Columbia University in New York and Alfred Hospital in Australia has demonstrated that prolonged IT (average 5 hours) did not adversely affect immediate or long-term survival or the incidence of transplant coronary artery disease [53,54]. The University of Western Ontario in Canada and The University of Alabama at Birmingham have also demonstrated that long-term survival of HTx was not affected by prolonged IT (longest times 457 minutes and 479 minutes, respectively) [55,56].”

2.12.2.3. 11c—Rationale for conclusions (including assessment of cause and effect)

- Statin-associated weakness in myasthenia gravis: a case report [57].

“The actual incidence of statin-exacerbated myasthenia is unknown, and only a handful of reports of statin-associated myasthenia gravis have ever been described. Out of six published case reports, only five patients were noted to have some degree of recovery and only one patient had a complete recovery upon termination of statin therapy.

How statins could appear to exacerbate MG is unclear. It is possible that the mechanism actually reflects a ‘double hit’ phenomenon of defective neuromuscular transmission secondary to antibody-mediated postsynaptic acetylcholine receptor dysfunction in combination with a statin-induced myopathy.

The clear development of a statin myopathy with simvastatin treatment before the onset of myasthenia in our patient is consistent with the possibility of a second (atorvastatin-induced) myopathy coalescing with the onset of myasthenia gravis. The symptomatic improvement that followed his withdrawal from atorvastatin treatment resulted from the resolution of this statin myopathy.

We also considered other potential causes of deterioration such as sepsis, steroid-induced worsening of MG, steroid myopathy, and cholinergic crisis, but we considered their development less likely based on clinical grounds.

We cannot rule out completely the possibility that the worsening of our patient’s MG simply reflected a progression of his MG. However, the clinical course of his condition, as well as the statin-induced proximal limb pain and weakness (without bulbar features) he experienced before his presentation, raises at the very least the possibility that a component of his initial deterioration was statin related.

Similarly, we note that his improvement could have reflected the immunosuppressive effects of therapy for his MG rather than the withdrawal of his atorvastatin treatment. It seems probable, however, that both factors played a significant role in the improvement of his clinical state.

The development of other autoimmune disorders such as dermatomyositis, polymyalgia rheumatica, vasculitis, and Lupus-like syndrome upon initiation of statin therapy raises the possibility that in predisposed individuals, statins may precipitate an immunological trigger that is analogous to penicillamine-induced MG although clearly different in temporal respect. However, given the paucity of reports and the widespread use of statins, the possibility of chance association cannot be excluded still.”

2.12.2.4. 11d—Main “take-away” lessons of this case report

- Prolonged unassisted survival in an infant with anencephaly [58].

“This infant met the diagnostic criteria of the Medical Task Force on Anencephaly. Therefore, she was the longest surviving anencephalic infant who did not require any life-sustaining treatments such as intubation or feeding tubes. Knowing this rare possibility, the physician and family should make goal-oriented decisions on how to care for the infant. The provider should offer immunizations and well childcare to each family if the infant survives the immediate newborn period. This case should affect the practice of physicians who interact with expectant mothers of a child affected by anencephaly.”

2.13. Item 12. Patient perspective section

CARE Checklist description: When appropriate patients should share their perspectives on the treatments they received.

2.13.1. Explanation

Whenever possible and relevant, provide patients with an opportunity to briefly share their perspectives on the episode of care. They may describe their motivations for seeking care, changes they associate with an intervention, or the impact of care on their quality of life. The report of a truly novel treatment may rely heavily on a patient’s perspective. Patients can be coauthors, which may require additional consent, owing to the loss of anonymity. A proxy, such as the parent of a minor, can provide a perspective when appropriate. In some cases, the line is blurred, and the author—usually a clinician—is also the patient [59].

2.13.2. Example

- Chronic rhinosinusitis and irritable bowel syndrome: a case report [60].

“I am a very active person and enjoy playing tennis and gardening. My symptoms before coming to George

Washington (GW) Center for Integrative Medicine prevented me from participating in the leisure activities that I enjoy. The quality of my sleep and my overall quality of life were not good. After coming to the GW Center for Integrative Medicine, all of my symptoms improved and I experienced a drastic improvement in my quality of life.

I did not follow an ‘elimination diet’ per se, but rather was instructed to follow a diet with foods to avoid based on my testing. I experienced a relapse of my sinus symptoms when I deviated too much from the diet, but am now able to control the symptoms by adjusting my diet accordingly.”

2.14. Item 13. Informed consent section

CARE Checklist description: Did the patient give informed consent? Please provide if requested.

2.14.1. Explanation

Informed consent is customarily required by medical journals. Whenever possible, obtain signed consent to write and publish the case report from the patient. Some cases may require additional consent (e.g., when potentially identifiable information is unavoidable, when the patient is older than 90 years of age in the United States, there is a photograph or image or has a rare disease).

In exceptional circumstances or if the patient is unable to provide consent, consent may be obtained from a close relative. For children who are too young to consent themselves, obtain consent from a guardian.

Case reports often include a statement that signed consent was obtained from the patient or if it is impossible to receive consent that all possible attempts were made.

2.14.2. Examples (journal informed consent guidelines)

- BMJ Case Reports - <http://casereports.bmj.com/site/about/guidelines.xhtml#patientconsent> (Accessed October 22, 2016) [61].

“Patient consent

Publication of any personal information about an identifiable living patient requires the explicit consent of the patient or guardian. This is a requirement under the UK’s Data Protection legislation. We expect authors to use the BMJ consent form which is available in several languages.

You must have signed informed consent from patients (or relatives/guardians) before submitting to BMJ Case Reports. Please anonymize the patient’s details as much as possible, for example, specific ages, ethnicity, occupations. For living patients, this is a legal requirement and we will not send your document for review without explicit consent from the patient or guardian.

If the patient is dead, the Data Protection Act does not apply, but the authors must seek permission from a relative (ideally the next of kin).

If you do not have signed consent from a deceased patient, guardian, or family, the head of your medical team/hospital or legal team must take responsibility that exhaustive attempts have been made to contact the family and that the paper has been sufficiently anonymized not to cause harm to the patient or their family. You will need to upload a signed document to this effect.”

3. Discussion

Case reports document the opportunities and challenges associated with the care of individual patients and empower clinicians to document care through scholarly contributions in peer-reviewed medical journals [4]. Evidence-based medicine also focuses on individual patient care through the integration of “clinical expertise with the best available external clinical evidence from systematic research.” [62] Experienced clinicians combine clinical expertise (the judgment and skill acquired through patient care) and external evidence as part of the recipe for providing better care to their patients. We believe that using the CARE reporting guidelines in case reports can facilitate and document the integration of evidence with expertise to inform clinical research, clinical practice guidelines (CPGs), and medical education [63].

Clinical research is driven by hypotheses. The evidence that hypotheses are not false is associated with the prior probability of an association between variables—for example, a diagnostic single nucleotide polymorphism test and a disease [64,65]. We believe that high-quality case reports offer supporting evidence regarding prior probability which may reduce the number of false-positive or false-negative findings. Case reports, and the systematic review of case reports [66], also provide information that informs CPGs [67].

Medical education uses problem-based teaching to cultivate clinical reasoning skills, first with evidence-based case simulations [68] and continuing with teaching rounds [69]. We believe that high-quality case reports provide real-world examples that can enhance critical thinking, improve documentation of patient care, and create life-long learning skills.

Case reports following the CARE guidelines

- Retrospective, practice based
- No protocols or controls
- Systematic data collection
- Consent required before publication.

4. Limitations of case reports

While case reports have the potential to detect signals of causal relations [51,70], they usually cannot exclude the possibility of a chance association. The selection of patients

whose care makes up most case reports is subject to selection bias and may represent outliers in clinical practice, necessitating caution regarding the generalizability of results [71]. N-of-1 studies (see Tables), which are protocol-driven, prospective trials [72]; case reports focusing on a pattern of physical, biological, or psychological phenomena integrated as a functional unit; or case reports that include rechallenge with a potential causal agent [73], may identify a causal relationship.

N-of-1 trials

- Prospective, research, or practice based
- Protocols and controls
- A priori consent required
- Optional patient input into design

Accurate and transparent case reports are challenging to write and publish. Medical records are often incomplete, inaccurate, or difficult to access, relevant interventions from other practitioners may be unavailable, and follow-ups are often not adequately documented. Published case reports are not cited as often as meta-analyses or randomized controlled trials and have a limited impact on academic advancement [74]—these factors may limit the number of case reports written and therefore published.

5. Conclusion

This explanation and elaboration document was developed to annotate the CARE Checklist, provide examples of good reporting, and address some of the limitations often associated with case reports. Systematic data collection from the point of care is now feasible; case reports following reporting guidelines can help offer the correct intervention to the right patient at the right time. We believe that case reports have the potential to offer evidence from the point of care that can be useful for clinical research, inform clinical practice guidelines, and improve medical education.

Acknowledgments

Contributors to the CARE Guidelines include the following: Altman DG, Aronson JK, Barber MS, Biswas S, Gagnier JJ, Hanaway P, Hayes CM, Helfand M, Kaszkin-Bettag M, Kiene H, Kienle GS, Kligler B, Koch C, Mittelman M, Moher D, Plotnikoff G, Riley DS, Rison R, von Schoen-Angerer T, Shamseer L, Smith R, Sox H, Sudak N, Sun GH, Tugwell P, Vohra S, and Werthmann P.

Author’s contribution: D.S.R., M.S.B., J.J.G., G.S.K., D.M., and L.S. developed the format for this article with input from other coauthors. The coauthors participated in the development of the CARE guidelines, offered insightful suggestions, and reviewed this manuscript. D.S.R.

organized the writing of this manuscript and the publication process with input from M.S.B., J.J.G., G.S.K., and other coauthors.

References

- [1] Vandembroucke JP. In Defense of Case Reports and Case Series. *Ann Intern Med* 2001;134:330–4.
- [2] Aronson JK. Anecdotes as evidence. *BMJ* 2003;326:1346.
- [3] Sun GH, Aliu O, Hayward RA. Open-access electronic case report journals: the rationale for case report guidelines. *J Clin Epidemiol* 2013 Oct;66:1065–70.
- [4] Akers KG. New journal for publishing medical case reports. *J Med Libr Assoc* 2016;104:146–9.
- [5] McBride WG. Thalidomide and congenital abnormalities. *The Lancet* 1961;278(7216):1358.
- [6] CDC. Pneumocystis pneumonia – Los Angeles. *Morbidity Mortality Weekly Rep* 1981;30(21):250–2.
- [7] Rison R, Helfgott M. Acute paradoxical embolic cerebral ischemia secondary to possible May-Thurner syndrome and an atrial septal defect: a case report. *J Med Case Rep* 2013;7:172.
- [8] Driggers RW, Ho CY, Korhonen EM, Kuivaneen S, Jääskeläinen AJ, Smura T, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. *N Engl J Med* 2016;374:2142–51.
- [9] Kaszkin-Bettag M, Hildebrandt W. Case report on cancer therapies: the urgent need to improve the reporting quality. *Glob Adv Health Med* 2012;1(2):8–10.
- [10] Richason TP, Paulson SM, Lowenstein SR, Heard KJ. Case reports describing treatments in the emergency medicine literature: missing and misleading information. *BMC Emerg Med* 2009;9:10.
- [11] Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *Plos Med* 2010;7(2): e1000217.
- [12] Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley DS. The CARE Group. The CARE guidelines: consensus-based clinical case report guideline development. *Glob Adv Health Med* 2013;2(5): 38–43.
- [13] Galipeau J, Barbour V, Baskin P, Bell-Syer S, Cobey K, Cumpston M, et al. A scoping review of competencies for scientific editors of biomedical journals. *BMC Med* 2016;14:16.
- [14] Kienle GS, Meusers M, Quecke B, Hilgard D. Patient-centered Diabetes care in children: an integrated, Individualized, Systems-oriented, and multi-Disciplinary Approach. *Glob Adv Health Med* 2013;2(2):12–9.
- [15] Jenicek M. *Clinical case reporting in evidence-based medicine*. 2nd ed. London/New York: Arnold and Oxford University Press; 2001.
- [16] Wei J, Chang CY, Chuang YC, Su SH, Lee KC, Tung DY, et al. Successful heart transplantation after 13 hours of donor heart ischemia with the Use of HTK Solution: a case report. *Transplant Proc* 2005; 37:2253–4.
- [17] Gish DS, Baer JA, Crabtree GS, Shaikh B, Fareedy SB. Impending aortic aneurysm rupture - a case report and review of the warning signs. *J Community Hosp Intern Med Perspect* 2016;6(5):32217.
- [18] Cooper D. How to write an original research paper (and get it published). *J Med Lib Assoc* 2015;103(2):67–8.
- [19] Jha KN. How to write articles that get published. *J Clin Diagn Res* 2014;8(9):XG01–3.
- [20] Cohen H. How to write a patient case report. *Am J HealthSyst Pharm* 2006;63:1888–92.
- [21] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and Conference abstracts: explanation and elaboration. *Plos Med* 2008;5(1):e20.
- [22] Davidson A, Delbridge E. How to write a research paper. *Paediatrics Child Health* 2012;22(2):61–5.
- [23] Vandembroucke J. Case reports in an evidence-based world. *JR Soc Med* 1999;92(4):159–62.
- [24] Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a t-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (aids). *Science* 1983;220:868–71.
- [25] Labris G, Katsanos A, Karapetsa M, Mpanaka I, Chatzoulis D. Association between isotretinoin use and central retinal vein occlusion in an adolescent with minor predisposition for thrombotic incidents: a case report. *J Med Case Rep* 2009;3:58.
- [26] Green BN, Johnson CD. How to write a case report for publication. *J Chiropr Med* 2006;5(2):72–82.
- [27] Rison A. A guide to writing case reports for the journal of medical case reports and BioMed central research notes. *J Med Case Rep* 2013;7:239.
- [28] Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomized controlled trials published in medical journals? A Cochrane review. *Syst Rev* 2012;1:60.
- [29] Chang HC, Burbridge H, Wong C. Extensive deep vein thrombosis following prolonged gaming ('gamer's thrombosis'): a case report. *J Med Case Rep* 2013;7:235.
- [30] Gottlieb M, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously health homosexual men; evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981;305: 1425–31.
- [31] Lang TA, Talerico C, Siontis GC. Documenting clinical and laboratory images in publications: the CLIP principles. *Chest* 2012;141: 1626–32.
- [32] Dählback B, Carlsson M, Svensson P. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C. *Proc Natl Acad Sci* 1993;90(3): 1004.
- [33] Namas R, Marquardt A. Case report and literature review: Quinacrine-induced Cholestatic Hepatitis in undifferentiated connective tissue disease. *J Rheumatol* 2015;42:1354–5.
- [34] Rajakumar D, Rosenberg AM. Mycobacterium tuberculosis monoarthritis in a child. *Pediatr Rheumatol Online J* 2008;6:15.
- [35] Sevinc M, Basturk T, Sahutoglu T, Sakaci T, Koc Y, Ahabap E, et al. Plasma resistant atypical hemolytic uremic syndrome associated with a CFH mutation treated with eculizumab: a case report. *J Med Case Rep* 2015;9:92.
- [36] Cella D, Stone AA. Health-related quality of life measurement in oncology: Advances and opportunities. *Am Psychol* 2015;70(2): 175–85.
- [37] Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965;58(5):295–300.
- [38] Rison RA. Branch facial nerve trauma after superficial temporal artery biopsy: a case report. *J Med Case Rep* 2011;5:34.
- [39] Mora JR, Rison RA, Beudoun SR. Chiari malformation type I with cervicothoracic syringomyelia masquerading as bibrachial amyotrophy: a case report. *J Med Case Rep* 2015;9:11.
- [40] Gatselis NK, Skendros P, Ritis K, Dalekos GN. Severe liver involvement in two patients with long-term history of fever: remember familial Mediterranean fever. *BMJ Case Rep* September 5, 2016; <http://dx.doi.org/10.1136/bcr-2016-216941>.
- [41] Liu YJ, Du P, Rao J. Procalcitonin as a diagnostic and prognostic marker for sepsis caused by intestinal infection: a case report. *Eur Rev Med Pharmacol Sci* 2013;17(10):1311–3.
- [42] Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) Checklist and guide. *BMJ* 2014;7:g1687.
- [43] Morino T, Ogata T, Horiuchi H, Yamaoka S, Fukuda M, Miura H. Eight years of follow-up after laminectomy of calcium pyrophosphate crystal deposition in the cervical yellow ligament of patient

- with Coffin–Lowry syndrome: a case report. *Medicine (Baltimore)* 2016;95(31):e4468.
- [44] Thomson N, Ulrickson M. Maintenance eculizumab dose adjustment in the treatment of atypical hemolytic uremic syndrome: a case report and review of the literature. *Clin Case Rep* 2016;4(8):773–6.
- [45] Tucker M, Kekulawala S, Kent M, Mostafa S, Harvey R. Polysubstance-induced relapse of schizoaffective disorder refractory to high-dose antipsychotic medications: a case report. *J Med Case Rep* 2016;10:242.
- [46] Gupta S, Szerszen A, Nakhl F, Varma S, Gottesman A, Forte F, et al. Severe refractory autoimmune hemolytic anemia with both warm and cold autoantibodies that responded completely to a single cycle of rituximab: a case report. *J Med Case Rep* 2011;5:156.
- [47] Oberg E, Rempé M, Bradley R. Self-directed mindfulness training and improvement in blood pressure, migraine frequency, and quality of life. *Glob Adv Health Med* 2013;2(2):20–5.
- [48] Waqas M, Hadi YB, Sheikh S, Shamin SM. Acute cerebellitis successful managed with temporary cerebrospinal fluid diversion using a long tunnel external ventricular drain [EVD]: a long-term radiological follow-up of two cases. *BMJ Case Rep* April 25, 2016; <http://dx.doi.org/10.1136/bcr-2016-215631>.
- [49] Tamanna S, Ullah MI, Pope CR, Holloman G, Koch CA. Quetiapine-induced sleep-related eating disorder like behavior: a case series. *J Med Case Rep* 2012;6:380.
- [50] Aronson JK, Grahame-Smith DG. Altered distribution of digoxin in renal failure—a case of digoxin toxicity? *Br J Clin Pharmacol* 1976;3:1045–51.
- [51] Hauben M, Aronson JK. Gold standards in pharmaco-vigilance: the use of definitive anecdotal reports of adverse drug reactions as pure gold and high-grade ore. *Drug Saf* 2007;30:645e55.
- [52] Wicomb WN, Cooper DKC, Novitzky D, Barnard CN. Cardiac transplantation following storage of the donor heart by a portable hypothermic perfusion system. *Ann Thorac Surg* 1984;37:243.
- [53] Morgan JA, John R, Weinberg AD, Kherani AR, Copletti NJ, Vigilance DW, et al. Prolonged donor ischemic time does not adversely affect long-term survival in adult patients undergoing cardiac transplantation. *J Thorac Cardiovasc Surg* 2003;126:1624.
- [54] Briganti EM, Bergin PJ, Rosenfeldt FL, Esmore DS, Rabinov M. Successful long-term outcome with prolonged ischemic time cardiac allografts. *J Heart Lung Transpl* 1995;14:840.
- [55] Del Rizzo DF, Menkis AH, Pflugfelder PW, Novick RJ, McKenzie FN, Boyd WD, et al. The role of donor age and ischemic time on survival following orthotopic heart transplantation. *J Heart Lung Transpl* 1999;18:310.
- [56] Canter C, Naftel D, Caldwell R, Chinnock R, Pahl E, Farzier E, et al. Survival and risk factors for death after cardiac transplantation in infants: a multi-institutional study. *Circ J* 1997;96:227.
- [57] Keogh MJ, Findlay JM, Leach S, Bowen J. Statin-associated weakness in myasthenia gravis: a case report. *J Med Case Rep* 2010;4:61.
- [58] Dickman H, Fletke K, Redfern RE. Prolonged unassisted survival in an infant with anencephaly. *BMJ Case Rep* 2016; <http://dx.doi.org/10.1136/bcr-2016-215986>.
- [59] Lundberg GD. Sciatica: a Love story. *Medscape* 2016. Available at <http://www.medscape.com/viewarticle/870832?pa=E%2FGwLt8TMfUWnw3BlflsLO9A2GUJcoFu7jfPhdaDERlanqMZzygbkW2buiVWXxjF8SIv18zjYv73GUyW5rsbWA%3D%3D>. Accessed December 10, 2016.
- [60] Kogan M, Castillo CC, Barber MS. Chronic Rhinosinusitis and Irritable Bowel syndrome: a case report. *Integr Med (encinitas) J* 2016;15(3):44–8.
- [61] *BMJ Case Reports*. Available at <http://casereports.bmj.com/site/about/guidelines.xhtml#patientconsent>. Accessed October 22, 2016.
- [62] Sackett DL, Rosenberg WMC, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71.
- [63] Califf RM, Robb MA, Bindman AB, Briggs JP, Collins FS, Conway PH, et al. Transforming evidence generation to support health and health care decisions. *N Engl J Med* 2016;375:2395–440.
- [64] Wacholder S, Chanock S, Garcia-Closas M, Ghormli L, Rothman N. Assessing the probability that a positive report is false: an Approach for molecular Epidemiology studies. *J Natl Cancer Inst* 2004;96:434–42.
- [65] Ioannidis JPA. Why most clinical research is not useful. *Plos Med* 2016;13(6):e1002049.
- [66] Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, Van Den Ende J, et al. Severe strongyloidiasis: a systematic review of case reports. *BMC Infect Dis* 2013;13:78.
- [67] IOM (Institute of Medicine). *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press; 2011.
- [68] Barrows HS. A taxonomy of problem-based learning methods. *Med Education* 1986;20:481–6.
- [69] Irby DM. Three Exemplary model of case-based teaching. *Acad Med* 1994;69:947–53.
- [70] Kiene H, Hamre H, Kienle GS. In support of clinical case reports: a system of causality assessment. *Glob Adv Health Med* 2013;2(2):64–75.
- [71] Hay JE, Wiesner RH, Shorter RG, LaRusso NF, Baldus WP. Primary sclerosing cholangitis and celiac disease. A novel association. *Ann Intern Med* 1988 Nov 1;109:713–7.
- [72] Shamseer L, Sampson M, Bukutu C, Schmid CH, Nikles J, Tate R, et al. Cent group. CONSORT extension for reporting N-of-1 trials (CENT) 2015: explanation and elaboration. *J Clin Epidemiol* 2016;76:18–46.
- [73] Badalov N, Baradaran R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007;5(6):548–61.
- [74] Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study design in the health sciences. *JAMA* 2005;293:2362–6.