Optimizing case reports and case series: guidance on how to improve quality

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Abstract

Case reports and case series remain an important part of journals and are often first to document medical breakthroughs. This article reviews their characteristics, aims and limitations. It provides information on how to increase the validity of the bedside decision-making process that these studies report, using tools such as validated outcomes and split body or n-of-1 trials. A section describing tools to improve writing of case reports and case series provides suggestions for detailed reporting and good evaluation of novelty, validity and relevance. It includes general and *British Journal of Dermatology* specific guidance.

Case reports and case series are an important feature of many journals. A recent analysis of the British Journal of Dermatology (BJD) manuscripts showed that they represented 9% of the BJD papers in 2015.[1] Case reports are an immediate reflection of clinical practice and remain attractive to readers. They invite thought and speculation, remind readers of forgotten conditions and are relatively easy to write and read, but their important role in medicine can be overlooked compared to other study designs within the evidence pyramid. Case series are a step forward in terms of elaboration, especially if prospective, but they share many characteristics of case reports and most of the content of this paper equally applies to them. While these papers naturally have methodologically weaknesses[2], they have often been first to document medical breakthroughs.[3] Some examples are the initial description of AIDS and toxic epidermal necrolysis, new therapies such as cyclosporine for psoriasis and propranolol for haemangiomas and rare or delayed adverse effects of interventions such as the risk of multifocal leukoencephalopathy with efalizumab.[4]

From the journals perspective, case reports, however popular with readers, generally reduce the journals' impact factor.[1,5] This has led to many journals abandoning them altogether or at least to restrict the selection of cases to those with the highest impact on readers and the research field.

Case reports and series can serve different purposes in dermatology (Table 1). Sometimes they do not include new information, but act as an introduction to put a review into perspective or as a learning aid, increasing our proficiency as visually literate clinicians.[6] Cases can describe new unusual findings for common conditions or improve our knowledge about uncommon diseases. Exceptional reports lead to a new hypothesis and can be the starting point of further research.

Guidance for writing good reports is limited. Jenicek's textbook on case reporting in evidence-based medicine[7] is one of the few extensive texts on this topic. Important missing information is one of the frequent deficiencies[2] that can be improved

following available case report (CARE) reporting standards.[8,9] We believe that other aspects of writing a good case report can be learned and planned.

The objective of this paper is to help authors of case reports and case series to improve their manuscripts and their chances of getting them published. We provide background information on the definition and limitations of case reports and series, and then discuss tools to improve them, including some BJD-specific suggestions.

Definition and limitations of case reports and case series

Case reports, case series and cohort studies. Where are the boundaries?

Case reports and case series share many characteristics and limitations. Case series refer to any report of more than one case. Some of them are a retrospective description of noteworthy cases, while others are planned and prospective.

For papers that describe the association between an exposure and an outcome, it might be difficult to make a clear distinction between a case series and a cohort study. The main difference is that cohort studies define the sampling method and the population from which the cases are selected.[10] This permits the calculation of absolute risks. Case series cannot do this, because the source population and the sampling method are unclear. If you can clearly define the sampling method of your case series, you should aim to produce a small cohort study and guidance for cohorts might be more useful for you.

Not all case series report a follow-up, and many might also be cross-sectional studies with a poorly defined sampling method. Sometimes case series are wrongly labelled as case-control studies, if they have a control group. The main difference is that, in case-control studies, patients are sampled based on the presence of an outcome, and time is a subtle but integral part of the design: the aim being to measure the differences in

an exposure that takes place earlier. Again, a defined sampling method makes the difference.

Why do case reports and case series provide poor evidence?

Findings in case reports and case series are prone to the deleterious effects of chance and bias, particularly selection bias, information bias and publication bias.

The effect of chance is more noticeable when the number of patients is low. If we have a single case, findings can be the norm in the reference population or an oddity. With small case series we will not have power to detect differences in the risk of an outcome, especially if it is uncommon. Therefore, failure to observe an adverse effect in a small series is to be expected. Small series cannot define overall safety, but they may indicate a signal. The same is true for therapy. With low numbers of patients, apparent treatment success may be due to chance.

Selection bias affects any report from a larger population that may be cherry picked: is the population in the paper representative of the source population? An extraordinary outcome may be representative of a group or an aberration; and thus, the sampling method must be clear. Extraordinary patients at baseline are more likely to show normal results in larger follow-up studies, and this is referred to as regression to the mean.

Information bias refers to an error due to inadequate assessment of the results of a case report, frequently showing unjustified optimism. This bias is more likely when relying on fuzzy assessments of improvement or non-standardized patient-reported outcomes, rather than more reproducible outcomes, like complete resolution of disease, death, or validated scales.

Publication bias describes the common observation that positive findings overwhelm the rarely published negative reports.[7] Negative reports (lack of benefit or harm) teach us caution and balance the optimism inherent to positive reports, helping to

avoid unnecessary treatment attempts and their adverse effects. Negative therapeutic case reports rarely tell the whole story because no treatment works in everyone; hence we need follow-up case series. Publication bias is an important limitation of systematic reviews that include case series.

Given the low validity of case reports to detect associations, better designed studies are usually required to confirm their findings. What kind of study depends on the aim of the report. Unfortunately, this rarely happens, and there are often no further studies. Even in high-impact general medical journals such as the Lancet, case reports and series of new interventions lead to randomized controlled trials (RCTs) in about 25% of cases.[11] Despite this lack of additional more valid data, second, third and fourth line therapy in rare diseases is frequently informed by weak evidence from case reports or series, when better evidence is lacking.

How to improve your case report or case series?

Having described the inherent weaknesses in case reports and case series, how can we improve their quality? It helps to know in advance what to do to increase the validity of the report. At the time of writing up the case, your report can only be partially enhanced.

Before writing: improving case reports at the bedside

Just as you see the patient and think about writing a case report, a few simple measures can be very helpful. The best way to reduce the effect of chance is to increase the number of participants: can you include more patients and transform your case report into a case series (ideally prospective and consecutive) or a cohort study?

Reporting consecutive patients in a case series, instead of a selection of them, is important to reduce selection bias. This usually means a prospective study, but could

also be achieved using patients' records. You should also think of using a validated outcome measure instrument to describe the outcome that you are reporting.

There are more sophisticated tools to improve the validity of your report. For topical therapies without systemic effect, a split body study comparison (i.e. using a therapy on one side and no therapy on the other) increases the validity of the results. This can be randomized and blinded to the observer.

The timing of events is a standard argument for causation, and the effect of withdrawal of therapy and re-challenge can strongly support your message. A more sophisticated application of this approach is the single patient (n-of-1) trial. This method is useful if you are describing a disease that is chronic and stable and a fast and short-acting therapy with an easy to measure outcome and doubtful results. The approach involves successive periods of treatment with the drug or a placebo, in agreement with the patient and with proper consent, to find out if the therapy works or not. Periods of therapy should be randomized and blinded and results should be measured objectively. A dermatological example has shown that tetracycline decreases the number of new bullae in a patient with epidermolysis bullosa simplex.[12] Similarly to confirming effective treatment, n-of-1 trials can also confirm causality of adverse events, when symptoms disappear on exposure to placebo. There is good guidance on how to perform n-of-1 trials[12-15] , which do not require special authorization if they are used as a decision-making tool for an individual patient. If they go beyond compassionate use, and the trial is primarily used to evaluate a new therapy, it becomes a phase I/II study.[16] If in doubt, the local clinical ethics committee can advise. The main hurdle will be having a pharmacist to prepare the blinded drug and placebo. You might also need some help to analyse the results. Results of published n-of-1 trials can be merged using meta-analysis and this can help in the description of therapies for rare diseases.[17]

Writing your report: everything that is needed but not more

Aim for the right target: What is the message of your report?

The first step when you begin to write your case report is to have a clear message: what makes your case outstanding and justifies its publication? This will organize your report in a logical form and help select the appropriate journal. How would you classify your report into the groups described in table 1?

Having a clear message should lead to a well-defined line of reasoning in your paper. As in other types of scientific manuscripts, the contents should organize around this main idea: write a short introduction that points to this key question as an unsolved problem, answer it with your case, discuss its credibility and value in the discussion and give a final sentence with your main message in the conclusion. Focus on this and avoid loading up your paper with more, secondary, topics.

Not all journals will publish all types of case reports. Some do not have a clear policy, some want only original findings, others are willing to publish reports of very uncommon findings, and some prefer to publish reports that focus on education.

Under the current authors guidance, the closest the BJD has to an educational case report is a critically appraised topic (CAT). This is a formalized literature review that is framed by a clinical case, and its methods have been recently described.[18]
For reports that describe unusual findings or simple messages, the BJD has the Image Gallery section where the visually arresting and thought-provoking cases can be published. Lastly, if your report generates a new hypothesis, this is our preferred type of manuscript for the case reports section. Due to their improved validity, n-of-1 trials are a welcome methodology for reports in the BJD. Examples in table 1 can also help you decide on the best BJD section for your paper.

Having a clear message and submitting your paper to the right section of the journal is the first step to improve your chances of publication. The second step is writing a clear and detailed manuscript.

Help users of the case report: give all the information, using available tools

Who might use your case report? Clinicians might look for the information that you report to apply it to their patient and researchers might consider adding your paper to a review, or testing your hypothesis in a study. Give enough details to ensure that both types of readers will find the information that they need. Many reports suffer from lack of detail, such as incomplete description of the intervention or follow-up, where it could easily be supplied.[2] Reviewers will check that your case report is detailed, new, valid, and relevant.

Description of the case: ensure detailed reporting

When describing the case or case series, use existing tools to ensure complete reporting. Many reporting guidelines are available through the EQUATOR network.[19] CARE guidelines are specific for case reports and include a useful template.[8] They cover the basic structure of case reports and are helpful for authors, but assume full length papers in conflict with space limitations of journals. As a consequence, many dermatology journals cannot fully comply with CARE guidelines.[20] There are general guidelines for complete description of interventions [21] and extensions on specific interventions of guidelines for randomized controlled clinical trials. An easy check to assure replicability is to show your report to a colleague and ask if they could replicate the intervention. If you are reporting an adverse effect, certain details are vital and authors should follow specific reporting guidelines[22] to optimize the discussion of alternative causes, drug details, or drug interaction. Describing if you have reported your case to the pharmacovigilance system is important to avoid double counting of events.

The discussion: is it new?

The discussion section of a case report is the place to highlight the contribution of your paper to the literature. From personal experience, the causes for the last 177 immediate rejections of case reports in the BJD were lack of novelty (23%), lack of validity (16%) and unclear relevance (8%), or a combination of these reasons (52%). Try

your best not to fall into these categories, but do not exaggerate. Unfounded claims are easily recognised, and annoy reviewers, editors and readers.

Are you reporting something new? Describe your findings in the context of previous knowledge. You should be exhaustive in the appraisal of the literature on the topic before submitting. We suggest that you use validated literature search filters to search for previous reports. The InterTASC Information Specialists' Sub-Group Search Filter Resource is an excellent, regularly updated resource.[23] Adding a reference for the search filter you used, or adding your search strategy as a supplementary material could help readers judge if your search was comprehensive. Claims of 'firstness or uniqueness' are usually unnecessary hyperbole and subject to challenge. "We have no found previous descriptions of XX" is better than claiming that yours is the first description. If there are previous reports, describe what your report adds to previous ones and concisely compare it with them.

The discussion: comment on validity and relevance

Validity needs to be addressed. Criteria are more stringent for case series that should discuss the effect of chance using confidence intervals, and attempt to define an underlying population and describe selection bias.

What is the effect of chance in your results? If you report several cases, whether on your own or as a review of published cases, use 95% confidence intervals to highlight the effect of chance. A new therapy that improves 6 of 8 patients (75%) may seem impressive, but a 95% confidence that ranges from 35 to 99% improvement rate curbs over-enthusiasm. The rule of three is a simple estimation[24,25] that can be used for series with zero events. Absence of adverse events is frequently seen when discussing safety in a case series. As an example, 20 patients with previous hepatitis B infection were treated with biologics, and none showed a reactivation of infection.[26] While common sense suggests that 20 is a small number, the rule of three indicates that the upper 95% confidence interval in the sample is 3 cases out of 20 (3/n), or 15%. The

correct interpretation of that paper is that the findings are compatible with up to a 15% reactivation of infection, and this should be highlighted in the discussion.

Any confidence interval is only as useful as the data it describes. Authors should provide information to help understand the magnitude of selection bias: did cases come from a single institution or from several departments? Were they collected in a primary care or specialized setting? How were patients identified? Were they collected from memory or by searching specific databases? Which patients may have been missed? Did you report all those that responded to therapy or those that received it? As a rule, all consecutive patients should be reported.

Further discussion about validity can make use of timing of events and the expected outcomes. Description of an association between improvement and the intervention is not a proof of causation, and you need to convince the readers of the validity of your observation. A timeline that clarifies the temporal correlation is frequently helpful, the CARE guidelines give some guidance on how to write these timelines.[27] Knowing the natural course of the disease or the usual response on standard treatment is key information. All or nothing effects provide more compelling evidence.[28]

Usually a lengthy part of the discussion that can free up space for needed clinical details are the speculations about a mechanism of action.[2]

Discussion of analogous situations can also be helpful. Similar outcomes to similar exposures can be discussed, ideally based on clinical results. Any marketed therapy has plenty of clinical data available that can be referenced and might be useful in new indications.

When the value of the data has been established, you need to explain the relevance of your report. What are the practical consequences of your paper? What is the hypothesis that can be derived from your report and what is the next step to evaluate

it? This may be a larger series or small cohort study; it is not usually a randomized controlled trial.

Conclusion

Case reports and case series are here to stay. They provide immediate exposure to new developments and stimulate original ideas, but are prone to bias and over-generalisation. Their role and relevance should not be undervalued, but all efforts should be made to improve their standards by using existing tools.

Table 1. The purpose of dermatological case reports and case series with examples

Purpose	Comments	BJD example
Case reports that do not provide new information ("reminders")		
To teach using cases	No new information. 1. They may simply remind of a finding/diagnosis 2. The key message is the review. CAT (Critically appraised topic) is a form that merges a case report framing a clinical question with a formalized review	1. Image Gallery: Nail involvement in syphilis: the great forgotten[29] 2. Is Mohs micrographic surgery more effective than wide local excision for treatment of dermatofibrosarcoma protuberans in reducing risk of local recurrence? A Critically Appraised Topic[30]
Case reports that provide some new clinical information		
To increase our clinical knowledge about known diseases	Three main types: 1. Describing unusual presentations of common disorders: "the tails of the normal curve" 2. Improving description of uncommon disorders or findings, usually through a case series 3. Description of associations (some may be due to chance)	1. Massive localized lymphoedema[31] 2. Skin manifestations among GATA2-deficient patients[32].(case series) 3. Pyoderma gangrenosum associated with azacytidine[33]
Case reports that lead to new hypothesis		
To describe new dermatological conditions	A novel disease or clinical finding, including results of	A foot tumour as a new form of late Lyme

or findings	tests	disease[34]
To describe new dermatological therapies		Granulocyte and monocyte apheresis for juvenile generalized pustular psoriasis with mutation of the IL36RN gene[35]
To describe new adverse effects of therapies	Rare adverse effects might not appear in randomized clinical trials or cohorts, and might only be described in case reports	Teriparatide used for osteoporosis and leading to worsening of calcinosis[36] (case series)
To provide insights into the mechanisms of disease	Some reports describe findings that could provide new hypothesis for pathophysiological research	Small-fibre neuropathy as a possible explanation of severe scalp pruritus in dermatomyositis[37]

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