

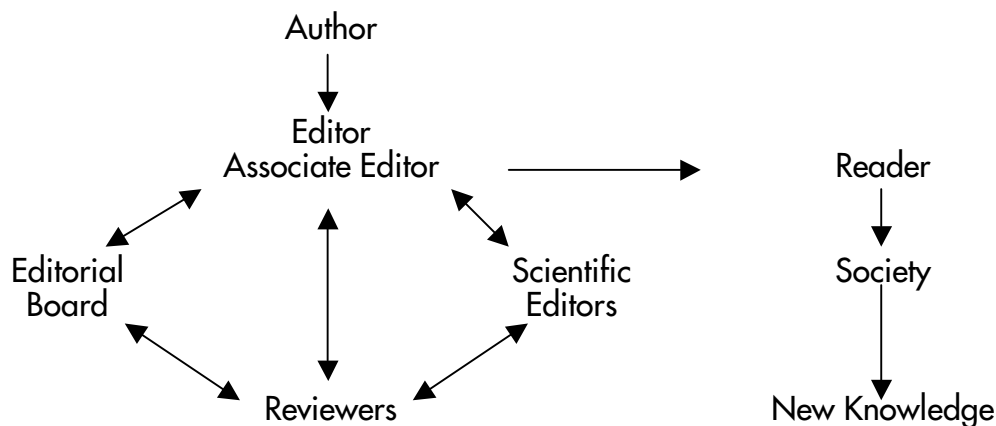
"How To Be a 5-Star Scientific Journal Reviewer"

Richard T. Scheife, Pharm.D., FCCP, Editor-in-Chief
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Peer Review

- ◆ What is the purpose of peer review?
- ◆ What will it never catch or detect?

Function of Reviewers



Online Submission and Review (Reviewer Interaction with Manuscript Central)

- ◆ Invitation to review from the Editor-in-Chief or a Scientific Editor
 - Abstract sent to reviewer with invitation letter
- ◆ Reviewer accepts or declines invitation
- ◆ New reviewer logs on to Manuscript Central and creates a reviewer account
 - Contact information
 - Areas of expertise
 - Customize availability parameters
- ◆ Reviewer views or downloads complete manuscript
- ◆ Reviewer may review manuscript online (piecemeal or all at once), or create the review offline (as a Word document) and "cut and paste" review into the Manuscript Central "reviewers' comments" section (do not attach the Word file)
- ◆ Reviewer has the opportunity to provide both "confidential comments to the editor" and "comments to be shared with the authors"

◆ Copies of all of the reviewers' comments will be sent to each reviewer when the "accept/reject" judgment is made. A reviewer's identity is never revealed to authors or other reviewers.

Journal's Responsibilities to Reviewers

- ◆ Inform reviewers of what you need
 - Examples of reviews
 - Review format
 - Reviewers' styles
- ◆ Time sensitivity
- ◆ Ongoing teaching by example
- ◆ Acknowledge and document contribution of reviewer to scientific literature
- ◆ Three areas of scholarly pursuit
 - Original research
 - Publication in peer-reviewed journals
 - Invitation to serve as an academic reviewer

Reviewer's Responsibilities to Journals

- ◆ You have responsibilities to both the author and the editor
- ◆ Pursuit of "truth and beauty"
 - Is this good science?
 - What is the impact of this paper?
- ◆ Filter out flawed work and prevent its publication
- ◆ How can non-fatally flawed papers be made more perfect?
 - Evaluate originality, quality, importance of paper
 - Identify errors, misinterpretation, overinterpretation, and "crimes of passion" committed by the authors
 - Fill in gaps (missing information)
 - Support your comments with appropriate references, if necessary
 - Make potential conflicts of interest known to the editor
 - Point out areas in which you are not qualified or comfortable to critique (keep in mind, absence of comments on, for instance, study design or statistics, infers correctness)
 - Inform us if you have previously reviewed this paper for another journal
 - In addition to identifying faults, positive comments are encouraged, when appropriate
- ◆ Line-by-line comments on grammar are not necessary; a global comment is all that is needed (e.g., "many spelling errors," "text is very difficult to follow")
- ◆ Timeliness in the completion of your review is essential
 - Kindly extend the courtesy of informing the journal immediately if you cannot review the manuscript in the allotted time
 - Your recommendation of another qualified reviewer is always appreciated

Sample Reviews

Sample review of a paper with a sufficient number of serious flaws that the reviewer's time and talent should not be expended at this point

Currently, the paper is so poorly written, from spelling and grammar to poorly presented material, it is painful to even read through it. There are so many poorly written sections I cannot even spend the time required to give specific comments. You might send it back to the authors and tell them it is not "finished" enough to be considered. Even if they had a competent editor make all these corrections, I find it difficult to believe that many readers would take the time to read through the paper. There is way too much text, and the details they have chosen to include are largely small, insignificant studies of "special populations." Putting this information into a table would be fine, but including it in the text just detracts from more relevant information. Also, this will save them the effort of rewriting their poor descriptions of these studies (see page 29, last paragraph, for a particularly bad passage).

On the other hand, although there are many reviews of atypical antipsychotics right now, none are as practical as they could be in terms of helping clinicians choose among the available typical and atypical medications. So it would be useful for you to publish such a practical review. However, this is the worst review I've read so far, and would require substantial revisions to make it into a practical review.

In case you offer the authors the opportunity to make the major revisions necessary for publication, I've included some general suggestions for them on a separate page.

Sample Review #1

The paper by XX et al. presents results from a retrospective cohort study based on FY2000 VA data evaluating a potential beneficial effect of statins and ARBs on 30-day mortality in patients hospitalized with sepsis. The study addresses a novel question of significant importance, is well written, and uses largely appropriate methodology (see comments below for an important suggestion regarding the analysis). The results are presented appropriately given the limitations inherent in the observational nature of the study, but the limitations, specifically a potential healthy user bias, need to be discussed in more detail.

Major comments:

1) The study presents results for statin-users vs. non-users and ARB-users vs. non-users. However, table 1 compares statins or ARBs (combined) vs. non-users. Present table 1 for the actual 3 groups (i.e. statin users, ARB users, non-users) and add a row to present the percentage of combination users.

2) On page 6 the authors present a sample size calculation. This is not meaningful to me since the study at hand is a retrospective evaluation of a database containing fiscal year 2000 VA records, originally compiled for a different study. If at all, a power calculation for a hypothesized effect size or -better- a calculation of the effect size detectable with 90% power, given the parameters of the data, would be informative. However, since the results for both drugs are significant, the entire section may be omitted.

3) The major limitation of the observational nature of the study is the potential for unmeasured confounders being responsible for the observed results. While the authors control for a number of potential confounders, including hospital, classes of medication, and Charlson comorbidity score, unmeasured confounding remains the main concern with this study. Specifically, the issue with the present study is a potential 'healthy user bias' (even after the adjustment for the aforementioned variables). The fact that medications that largely treat asymptomatic, chronic conditions (e.g. statins) are underutilized in patients with unrelated comorbidities(1) may lead to a healthier population of users of a chronic medication. While the authors mention this limitation in the discussion section, they should expand on the discussion since this potential bias is the key issue with this paper. For example, Glynn et al showed that a relatively modest association of unmeasured frailty with the exposure to lipid lowering drugs (after propensity score adjustment) could explain an observed beneficial effect of these medications on mortality.(2) Researchers have addressed this problem by using a comparison group of users of another chronic medication, instead of a group of non-users of the drug under study. For example, while Ray et al showed a significant 38% (15-55%) reduction in the risk of hip fractures among new users of statins compared to non users, this beneficial effect disappeared when the comparison was made between new statin users and new users of other lipid lowering drugs (RR: 1.42; 0.83-2.43).(3) Similarly, in a study investigating a hypothesized beneficial effect of statins on the risk of lung, breast, and colorectal cancer, Setoguchi et al. used a comparison group of new users of glaucoma medication (instead of non-users). Thus, ideally, the authors

may want to consider replicating the analysis with a control group that would have a similar user profile (e.g. patients on non-statin lipid lowering drugs or glaucoma medication).(4) If the beneficial effects of statins and ARBs remain significant compared to users of other chronic medications (that don't have a biologically plausible beneficial effect on patients with sepsis), the paper would be strengthened considerably, if not, a healthy user bias would be the likely explanation for the apparent protective effects of both drugs. At the very least, the potential healthy user effect should be discussed in more detail referencing the previous research.

Minor comment:

For completeness: Start the methods section in the article in a way similar to the abstract methods (i.e. define the study as a retrospective cohort study)

References

1. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med.* May 21 1998;338(21):1516-1520.
2. Glynn RJ, Schneeweiss S, Wang PS, Levin R, Avorn J. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. *J Clin Epidemiol.* Aug 2006;59(8):819-828.
3. Ray WA, Daugherty JR, Griffin MR. Lipid-lowering agents and the risk of hip fracture in a Medicaid population. *Inj Prev.* Dec 2002;8(4):276-279.
4. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation.* Jan 2 2007;115(1):27-33.

Sample Review #2

Your manuscript is a MASSIVE work! I cannot fathom how many hours you have invested in tracking down all of these studies / reports, and compiling them into your paper. Goodness!

I have read this paper several times and submit these recommendations to you:

1. Your manuscript needs to be substantively reconstructed in order to be usable to the Journal's audience.
2. In print, this article's utility will be as a reference for pharmacists dealing with plasmapheresis. Readers will be seeking to manage one of two scenarios:

* A patient may be considered for plasmapheresis in the setting of acute toxicity, in which case the question is whether or not PE will contribute substantively to total drug clearance, OR

* A patient will be receiving PE either once or chronically for treatment of an immunologically-mediated condition. In this case, the pharmacist will be wondering whether replacement doses of chronic medications will be necessary.

Your article MUST address each of these situations in order to be useful to the reader; thus, I strongly encourage the authors to reformat their submission with the clear intent of addressing these two questions.

3. You are correct in your assertion that the literature on PE is scattered and non-uniform in its reporting of data. You however, must be our saviour and amend this! Lucky you! What I mean by this is that, in order for your information to be readable and useful, you must determine a:

- * standard format of TYPE of information included, and
- * a standard format of MANNER in which it is presented.

For examples: some of these data are presented as "percent of circulating drug removed", some as "percent of total daily dose removed", some as "fraction eliminated"...etc. You MUST be prepared to do more than just rewrite the data; you need to offer your own interpretation as to whether or not,

- a) Total body removal of drug is substantial enough to warrant use in toxicologic emergencies, and
- b) Total body removal of drug is substantial enough to warrant alterations in dosing in patients receiving PE on a chronic basis. This will need to include the pharmacodynamics of drug response in addition to simply the kinetics of drug removal. What I mean to say is that, for some drugs, even if the entire last dose is removed, does it really matter in terms of dynamic response? You'll need to look at half-life (time to reaccumulate), dosing intervals.....lots of things in order to make this a useful guide to drug dosing in PE patients.

4. Your paper will need to include a substantial introduction that explains several things to the reader:

a.) What is PE, exactly? How does it "work"? In what circumstances is it employed? How frequently is it employed? Do all institutions have access to PE? Is it considered standard of care or is it still controversial?

b.) How is drug removal by PE accomplished? This is huge!!! You MUST distinguish how drug removal by PE is different from drug removal by hemodialysis. You must discuss both plasma and tissue protein binding. You must discuss flow rate, run time, redistribution.....the whole potato, in order that your reader truly can understand the information you will present later. Pharmacists as a whole have no understanding of PE and so you get to be the one who teaches it.....otherwise, we will not understand the data you present. (Sorry!)

5.) Tighten up your Table 1: For each drug, include the "bottom line" for each of the two questions described in recommendation # 3a above. Keep terminology standard from item to item or include a brief explanation. Avoid terms like "circulating drug". This is useless. Use either total body drug or pre and post redistribution concentration change, or fraction of dose eliminated.....

6.) You'll need to also include a discussion of terms. How are "total body stores" estimated? Is this a reliable calculation (estimation)? Your reader will not know. Be careful with terms like "fraction eliminated was 10%". Fraction of what? Total stores? Single dose? Plasma drug concentration? Your readers will need a mini kinetics primer in order to understand what you are telling them....but it IS doable.

7.) Finally, I recommend that you NOT include a drug-by-drug discussion in the body of your manuscript. Use the body of your text to discuss the issues clinicians will need to understand in order to make a decision based upon your information. Put the drug-by-drug information in the table, reference the studies, and be done with them. Yours is a synthetic and an interpretive function....not a data dump.....please. This article can be hugely informative. Please consider.

Sample Review #3

Overall this manuscript is a comprehensive and well-written paper concerning adrenal insufficiency. One could argue that the initial sections dealing with the pathophysiology through the clinical manifestations of adrenal insufficiency (as well as most of the tables and figures) could be deleted in the interest of journal space considerations since most of this is basic information that is not specific to the critically ill patient. On the other hand, it makes the paper comprehensive and more useful to the relatively inexperienced practitioner. The remainder of the paper hits the key literature with respect to the diagnosis and treatment of adrenal insufficiency in the critically ill patient and provides reasonable recommendations for practice based on this literature.

Unfortunately for the author, the results of a couple of important studies have just been presented within the past few weeks that need to be added to the paper to stop it from being outdated soon after publication. In particular, the results of the CORTICUS trial were presented as late breaking sessions at the SCCM February meeting (as well as the ATS meeting if I'm not mistaken). This multi-center blinded RCT found no significant difference in mortality between low-dose hydrocortisone and placebo in cortrosyn non-responders, the group thought most likely to benefit from steroids based on the trial by Annane et al. In fact, the hydrocortisone group tended towards higher mortality, and hyperglycemic and infectious complications were also more frequent. The lack of even a trend towards benefit in the steroid group offset the fact that the trial had to be stopped (at 499 analyzable patients) before the anticipated enrollment of 800 patients. Furthermore, when the lead investigator, Dr. Sprung, presented the findings at SCCM, he concluded that the results also suggested that routine ACTH testing is not indicated. The CORTICUS trial will clearly not end the debate concerning the use of steroids in septic shock since there were some differences in the methods and results of the Sprung and Annane trials (e.g., severity of illness, use of fludrocortisones). Regardless, the initial results of the CORTICUS trial are likely to be published within the next few months.

Another paper was presented at the SCCM meeting that likely will affect the statements in the last paragraph of the treatment section of the paper dealing with hyperglycemia. The GLUCONTROL study was another multi-center investigation comparing tight (80 to 110 mg/dL) vs. moderately tight (140 to 180 mg/dL) glucose control in the ICU. No differences were found in ICU or hospital mortality or length of stay. Furthermore, more patients in the tight control group suffered from episodes of hypoglycemia and the death rate in patients with hypoglycemia was higher in the tight control group. As above, this trial will likely not end the debate concerning tight glucose control.

The author should be able to get the preliminary results of both of these papers from meeting summaries and possibly the Internet (I think I saw the CORTICUS results on Medscape). Obviously, the paper would be more timely with the

inclusion of these studies, and the author may want to revise some of his conclusions based on these trials.

I have two specific, albeit minor issues for consideration.

Corticosteroids section, second to the last paragraph, third sentence. Since the terms hydrocortisone and cortisol are used interchangeably, I'm wondering if the author means that 10 mg/day of cortisol in the body is equivalent to 20-30 mg per of hydrocortisone given orally. If not, than another explanation is in order.

Table 6. I have mixed emotions about the need for this table. While it does provide a nice summary of the key tests for adrenal insufficiency, it repeats what is in the text yet does not provide some of the important qualifiers stated in the text, particularly for ACTH stimulation (so it's not really a stand-alone table).

Sample Review #4

The stated objectives of this manuscript are to describe the pharmacokinetics of pegfilgrastim and the ANC profiles after administration of the drug to patients receiving cancer chemotherapy. Though the information provided in this manuscript is interesting, the results do not accurately reflect the stated objectives and do not flow from the methods. The discussion seems to indicate that an objective of the paper was to evaluate the tempo of ANC response to pegfilgrastim administration in order to address the concerns of clinicians regarding the possibility of achieving dangerously high white counts. Serious revision of the manuscript is necessary to ensure that the stated objectives are met and that the methods adequately describe how the results were derived.

Introduction:

The study objectives stated in the last paragraph of the introduction should be identical to those stated in the abstract (or vice versa). Those stated in the abstract are more in line with the title of the manuscript. That is, to describe the pharmacokinetics and ANC profiles after pegfilgrastim administration. Please align and clarify the objectives of your study.

When speaking about drug concentrations, please use the term 'concentration' rather than 'level'.

Methods:

Please be more clear in the text about which studies' data were used for which aspect of the study (PK vs ANC profile). For example the sentence that begins 'No pharmacokinetic data were collected. . ' on page 6 should be moved to the first paragraph.

Please define 'ANC profile' and 'nadir'. In addition, use of the term pharmacokinetics is confusing since no traditional PK data are presented. Do you mean only to describe the inter-relationship between serum pegfilgrastim concentrations and ANC? Please use a term other than pharmacokinetics to describe your data or provide methodology relevant to the determination of pharmacokinetics.

Please provide the number of patients who received each of the 2 dosing strategies. Did either the PK or ANC profiles differ between these groups?

ANC is more traditionally defined as the neutrophil count plus the band count. Why was this more accepted definition not utilized? In addition, the word 'cells' is usually inserted into the units for ANC; i.e. 1.0×10^3 cells/mL.

Mention of filgrastim as the 'comparator' drug on page 7 is confusing as no comparisons are made in this study.

On page 7 it is stated that the 'Average time course of ANCs was similar between cycle 2 and subsequent cycles'.

How was this determined?

In the last sentence of the Methods section, it is stated that Pearson's correlation coefficients were calculated for ANC. What was the second variable in this correlation? Which time points after pegfilgrastim administration were assessed? Please indicate that patients who experienced high ANCs following pegfilgrastim administration were specifically identified.

Results:

Please use all abbreviations in full the first time they are used in the manuscript.

It would be helpful if the results were presented in the same order as the relevant methods.

Please present data relevant to clearance and other pharmacokinetic parameters.

Please describe the methods relevant to the development of the biomathematical model used to determine the lowest pegfilgrastim concentration able to elicit meaningful granulopoiesis. This information should be included in the Methods section. Please also more fully explain the concept of EC values in the Methods.

Please give the actual number of patients as well as % who experienced a postnadir ANC $\geq 30 \times 10^3$ cells/mL.

Similarly, please provide correlation coefficients and p values in the text.

Discussion:

The first paragraph of this section provides important information required by the reader. However, its message would be clearer if the sentences were presented in a different order.

Tables

Please explain all abbreviations used in the tables in a legend for each table.

Figures:

Please refer to each figure in the text.

Figure 1: Are these graphs not concentration/count vs time graphs positioned to allow easy comparison rather than correlations? The figure title labels them as correlations.

Sample Review #5

This is an interesting case, but one which may have a flawed (and potentially dangerous) conclusion. It would greatly benefit this case, and its readers, if the authors discussed the different scenarios and controversies that might better explain their results (discussed below).

First, some general comments:

1. A graphic detailing the timeline of drug initiation, rash progression, eosinophilia, and concurrent medication use would significantly complement this case scenario. An example of such a graphic is Lynch J, Wong-Beringer A. Caspofungin: a potential cause of reversible severe thrombocytopenia. *Pharmacotherapy* 2004;24:1408-11.
2. On page 5, 1st paragraph. Believe you meant to say "In our report, the negativity of the skin test with amoxicillin and MEROPENEM...."

Comments about case:

1. Significantly more discussion is needed regarding the type of allergic reaction that the patient developed from the imipenem-cilastatin. This is crucial in order to convey safe, accurate information to readers. The implications are important: true anaphylactic hypersensitivity, which we presume is what the authors are implicating in this case, is IgE mediated, often immediate, and presents with urticaria, laryngeal edema, bronchospasm, hypotension, and/or local swelling. These are the reactions that are of most concern to clinicians, especially concerning cross-reactivity between antimicrobial agents of the same class. When it comes to skin testing, only penicillin skin testing (using major and minor immunogenic determinants) has been shown to be accurate for the identification of IgE-mediated hypersensitivity. A "positive" skin test from pure imipenem-cilastatin compound might not be due to IgE. This is an important distinction in this case, because the "erythematous macular morbiliform rash" that this patient developed after 5 days of imipenem-cilastatin is more consistent with a delayed-type hypersensitivity reaction, which is mediated through T cells, not IgE. (see Gruchalla RS, Pirmohamed M. Antibiotic allergy. *NEJM* 2006;354:601-9). This is NOT an anaphylactic reaction, and correlations regarding cross-reactivity concerning these reactions have not been made (see Brackett CC, Singh H, Block JH. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. *Pharmacotherapy* 2004;24:856-70). Presumably, the development of a 5mm wheal after a skin test with imipenem-cilastatin could be mediated by T cells (as in PPD skin tests). As such, the case as described now would confuse clinicians without significant knowledge of the types of allergic reactions, and perhaps could lead to meropenem use in patients with true IgE-mediated hypersensitivity to imipenem-cilastatin. This is a very dangerous scenario. The authors are correct that the Bauer reference (*J Allergy Clin Immunol*) does appear to reflect a case of true IgE hypersensitivity (large erythematous maculopapular rash developing within 48 hours, and possibly most important, with areas of urticaria). However, the present case might not reflect a similar situation, and in order for the authors to draw any conclusions, they must expound upon the scenarios presented above. Another point that is interesting is the eosinophilia in this case. It would be prudent for the authors to discuss whether this finding is indicative of an IgE mediated reaction, or may occur in other scenarios (for example, acute interstitial nephritis may present with eosinophilia, but is considered to be a Type II, ie IgG mediated, reaction).

Sample Review #6

1. Did the sponsor which makes atypical antipsychotics) have any role in initiating, designing, analyses or interpretation of study? Do any of the study authors work for the sponsor or have consulting or financial ties to any atypical manufacturers?

2. The title is misleading - the outcome looked at here was just a subset of all cases of pancreatitis - ie hospitalized diagnosed symptomatic pancreatitis. So the title and abstract and methods and discussion need to make this clear.

3. Introduction - the conclusions of Szarfman et al are misrepresented. That study did not report "an increased risk" but merely found differences in reporting ratios and concluded there may be differences even among atypical agents with clozapine and olanzapine having the highest reporting ratio. They also found that reporting was highest for individuals concomitantly using lithium or valproate. The authors need to correctly cite this paper.

The Methods is flawed for several reasons:

4) The total numbers of atypical and conventional users by specific drug (clozapine, olanzapine, risperidone, etc) is not specified and needs to be

5) It is inappropriate to pool all atypical users since there are differences among these agents in lipid and pancreatic effects. Given the lack of power to assess individual atypicals, all that can be concluded is that their sample is too small to test effects with atypicals. The number of conventional agent users (N=2000) is 10 times higher than the number of atypical agent users (N=200) giving rise to differences in statistical power as shown in their own highly variable confidence estimates.

6. There is no information on dose or duration of use. Atypical and conventional antipsychotics are often used for different populations and so controlling for age and gender alone will not suffice if the primary diagnosis for which they are given for is not taken into account.

7. The authors provide no data to assure that users of atypical and conventional drugs did not differ in other ways that would have biased their outcome. I suggest they provide a Table comparing the atypical and conventional users on age, gender, race, economic status, DSM or ICD psychotic diagnosis, duration of drug use, dose, diabetes, ethanol use, gall stone disease and use of concomitant lithium and mood stabilizers.

8. How was combination drug use of atypical and conventional addressed?

9. Most cases of pancreatitis are asymptomatic and numerous studies have now shown that drugs like clozapine and olanzapine induce asymptomatic pancreatitis during dose titration that can only be detected with enzyme testing. These studies also document reversal of enzymes upon cessation of the drug which suggest causative links. Such asymptomatic cases would not have been captured in this study.

10. the discussion of the discrepancy between their finding and those of the two prior epidemiological findings should be discussed more and should conclude with statement that neither their study nor those prior can prove causality. Only a definite prospective study can. Their abstract should also discuss the discrepancy between their study and two prior epidemiological studies.

11. Although the authors claim their methodologic validity has been established previously, I suggest they run an analyses looking at valproic acid, a known pancreatitis agent, as a positive control. If this agent is shown to have a pancreatitis effect then it adds confidence to their sample.

"How To Be a 5-Star Scientific Journal Reviewer"

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LEARNING OBJECTIVES

1. Discuss the purpose of peer review, and outline its advantages and disadvantages.
2. Describe the two general areas on which to focus when reviewing any kind of scientific paper.

SELF-ASSESSMENT QUESTIONS

1. Which of the following components is least useful to the editor for reviewers to include in their comments to an author?
 - a. Evaluate originality, quality, and importance of the paper.
 - b. Support comments with appropriate references, if necessary.
 - c. Provide positive comments when appropriate.
 - d. Provide line-byline comments on grammar.
2. All except which of the following are responsibilities that a journal has to its reviewers?
 - a. Inform reviewers of the review format.
 - b. Be time sensitive and limit the number of manuscripts sent to each reviewer.
 - c. Provide to reviewers the names of the other reviewers.
 - d. Update reviewers' areas of expertise as specifically as possible.
3. All except which of the following are responsibilities that a reviewer has to a journal?
 - a. Inform the journal if you have previously reviewed the manuscript for another journal.
 - b. Point out areas in which you are not qualified or comfortable to critique.
 - c. Make potential conflicts of interest known to the editor.
 - d. If you are unable to complete the review in the requested time frame, simply ignore the request for review, as the other reviewers will probably comply.

ANSWERS TO SELF-ASSESSMENT QUESTIONS

1. d
2. c
3. d