References cited in the clinical content are classified according to the type of evidence presented. The class ratings, I through V, are intended to provide a classification of the evidence but are not necessarily hierarchical. Classifications appear in parentheses at the end of each reference. References followed by an (NC) are not classified; examples include pre-published research or information from government, manufacturer, laboratory, or patient education websites.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Type of Evidence</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
<td>Meta-analysis, technology assessment, or systematic review</td>
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<tr>
<td>Class II</td>
<td>Randomized controlled trial</td>
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<tr>
<td>Class III</td>
<td>Observational or epidemiologic study</td>
</tr>
<tr>
<td>Class IV</td>
<td>Evidence-based guideline</td>
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<tr>
<td>Class V</td>
<td>Expert opinion, panel consensus, literature review, text or reference book,</td>
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<td></td>
<td>descriptive study, case report, or case series</td>
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</table>

Class I

Class I sources synthesize the results of multiple studies. When quantitative synthesis is possible, meta-analyses can provide a more accurate estimate of the effect or association size than individual smaller studies can. A Class I study that finds insufficient evidence to support or refute an intervention (due to a lack of appropriate primary research) is inconclusive. A potential weakness of Class I studies is that they may only assess published research, potentially leaving their findings vulnerable to publication bias.
Class II

A randomized controlled trial (RCT) is an experimental study design in which subjects are randomly assigned to an intervention or a control group. An RCT is the gold standard for testing cause and effect relationships. Intention-to-treat analysis should be performed to account for missing data points.

Class III

Observational or epidemiologic studies can suggest an association between events or findings. These associations cannot be used to establish causality. Cross-sectional, cohort, and case-control studies are all used to identify possible risk factors. Cross-sectional studies are also used to determine the prevalence of a condition. Cohort studies are used to study incidence, the natural history of a condition, prognosis after a specific exposure, and associated harms. Nonrandomized controlled trials are sometimes used when randomization is impossible or unethical.

Class IV

Evidence-based guidelines are systematically developed recommendations for clinical practice. Evidence-based guidelines identify the methodology used to gather the evidence on which the recommendations are based. Usually, a grading system for both the quality of the evidence and the strength of the recommendations is provided. Guidelines that are evidence-based may also contain consensus recommendations in areas where evidence is lacking, but these recommendations are clearly identified and appropriately graded.

Class V

Class V references may be the best information in the absence of other evidence. Expert opinion, panel consensus, literature reviews, and descriptive studies (case reports or case series) are subject to significant bias. A case series with comparison to historical controls can be plagued with missing data, and data extraction inconsistencies are common. The use of historical controls does not address how the diagnosis of disease or its treatment has evolved over time with newer technologies or medication. Textbook information may be out of date by the time the book is published.

Comparative Effectiveness Research (CER)

Citations are designated with the CER label as part of the evidence classification if the article cited is one of the following:

1. A clinical trial or other clinical study that directly compares two or more health care interventions for the same clinical scenario.

2. A systematic review that compares two or more health care interventions by synthesizing the research from previous clinical studies.
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