OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary
Antimicrobial Therapies for Infective Endocarditis

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BACKGROUND AND RATIONALE

Infective endocarditis (IE) is an uncommon infectious disease with an annual incidence ranging from 3 to 7 per 100 000 person-years in the most contemporary population surveys. Although relatively rare, IE continues to be characterized by increased morbidity and mortality and is now the third or fourth most common life-threatening infection. Before the advent of antibiotic therapy, infective endocarditis was fatal.[1]

Antibiotics delivered intravenously achieve rapid therapeutic concentrations in blood and perfused tissues, and they are generally regarded as more potent and reliable than oral antibiotics. For these reasons, intravenous (IV) antibiotics are considered the cornerstone of IE treatment. The recommended duration of IV antibiotic therapy for IE varies depending on the characteristics of the infecting organism and the affected endocardial structure but in no instance it is <2 weeks and in most cases it extends to 6 weeks. However, there are instances in which the options of effective IV antibiotics are limited, or the maintenance of prolonged intravenous access is not desirable (i.e. active intravenous drug users) or feasible. In these situations, oral antibiotic therapy may be an alternative. [1]

This evidence brief seeks to determine the optimal dosing and route of antimicrobial treatment in intravenous drug users (IVDUs) with IE.

ASK THE QUESTION

In IV drug users with infective endocarditis (IE), what is the comparative clinical effectiveness of various anti-microbial therapies?

SEARCH FOR EVIDENCE

Databases included: Ovid MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials

Search strategy included: MeSH terms: Endocarditis, Anti-Bacterial Agents

Filters/limits included: Articles published in English since December 2014

For full search Strategy please see Appendix A.

CRITICALLY ANALYZE THE EVIDENCE

The recommendations from the American Heart Association's 2015 guideline for the treatment of infective endocarditis as well as the update primary literature published since the guideline was released is included in the review. Only the general treatment recommendations and the recommendations pertaining to common microorganisms causing infective endocarditis in intravenous drug users are included in the analysis.

Two systematic reviews are included in the appraisal of literature published since the AHA guideline. Overall, there was low quality of evidence unable to determine the most effective treatment course and duration for infective endocarditis. Cure rates ranged from 89-100% in the clinical trials focusing on oral antibiotics and 32-100% in the trials including both oral and IV antibiotics. The duration of treatment ranged from 4-14 weeks.

External Guideline Recommendations:

American Heart Association's 2015 Guideline for Infective Endocarditis in Adults:

-Infectious diseases consultation should be obtained to define an optimal empirical treatment regimen at the time of initiation of antimicrobial therapy (Class I; Level of Evidence B)

-It is reasonable that the counting of days for the duration of antimicrobial therapy begin on the first day on which blood cultures are negative in cases in which blood cultures were initially positive (Class IIa; Level of Evidence C).

-It is reasonable to obtain at least 2 sets of blood cultures every 24 to 48 hours until bloodstream infection has cleared (Class IIa; Level of Evidence C).

-If operative tissue cultures are positive, then an entire antimicrobial course is reasonable after valve surgery (Class IIa; Level of Evidence B).

-If operative tissue cultures are negative, it may be reasonable to count the number of days of antimicrobial therapy administered before surgery in the overall duration of therapy (Class IIb; Level of Evidence C).

-It is reasonable to time the administration of antimicrobial therapy at the same time or temporally close together for regimens that include >1 antimicrobial agent (Class IIa; Level of Evidence C).

Epidemiological Feature: Intravenous Drug Use

Common Microorganisms: *S. aureus*, including community acquired oxacillin-resistant strains, Coagulase-negative staphylococci, β-Hemolytic streptococci, Fungi, Aerobic Gram-negative bacilli including *Pseudomonas aeruginosa*, polymicrobial

IE Caused by Staphylococci in the Absence of Prosthetic Valves or Other Prosthetic Material: Right-sided IE in IDUs

-Gentamicin is not recommended for treatment of right-sided staphylococcal NVE (Class III; Level of Evidence B).

-Gentamicin should not be used for treatment of NVE caused by MSSA or MRSA (Class III; Level of Evidence B).

-In cases of brain abscess resulting from MSSA IE, nafcillin should be used instead of cefazolin; vancomycin should be given in cases of nafcillin intolerance (Class I; Level of Evidence C).

-The usefulness of empirical combination therapy with vancomycin plus an antistaphylococcal β-lactam antibiotic in patients with *S aureus* bacteremia until oxacillin susceptibility is known is uncertain (Class IIb; Level of Evidence B).

-IE caused by staphylococci that are penicillin susceptible should be treated with antistaphylococcal β-lactam antibiotics rather than aqueous crystalline penicillin G because clinical laboratories are not able to detect penicillin susceptibility (Class I; Level of Evidence B).

-Six weeks of nafcillin (or equivalent antistaphylococcal penicillin) is recommended for uncomplicated left-sided NVE caused by MSSA; at least 6 weeks of nafcillin (or equivalent antistaphylococcal penicillin) is recommended for complicated left-sided NVE caused by this organism (Class I; Level of Evidence C).

-Daptomycin may be a reasonable alternative to vancomycin for treatment of left-sided IE resulting from MRSA (Class IIb; Level of Evidence B).

-Selection of daptomycin dosing should be assisted by infectious diseases consultation (Class I; Level of Evidence C).

Therapy for NVE caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafacillin or oxacillin	12g/24 h IV in 4-6 equally divided doses	6	Class I; Level of Evidence C	For complicated right-sided IE; for uncomplicated right-sided IE, 2 wk
For penicillin-allergic patients				
Cefazollin*	6g/24 h IV in 3 equally divided doses	6	Class I; Level of Evidence B	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases
Oxacillin- resistant strains				
Vancomycin	30mg/ kg per 24 h IV in 2 equally divided doses	6	Class I; Level of Evidence C	Adjust vancomycin dose to achieve trough concentration of 10-20 µg/mL
Daptomycin	≥8 mg/kg/dose	6	Class IIb; Level of Evidence B	Await additional study data to define optimal dosing

*Doses recommended are for patients with normal renal function

IE Caused by Staphylococci: Coagulase-Negative Staphylococci

-Ongoing vigilance for IE complications, including perivalvular extension of infection and extracardiac foci of infection, is reasonable (Class IIa; Level of Evidence C).

IE Caused by β-hemolytic streptococci:

-Consultation with an infectious diseases specialist to guide treatment is recommended in patients with IE caused by β-hemolytic streptococci (Class I; Level of Evidence C).

IE Caused by Fungi:

-Valve surgery should be done in most cases of fungal IE (Class I; Level of Evidence B).

-After completion of initial parenteral therapy, lifelong suppressive therapy with an oral azole is reasonable (Class IIa; Level of Evidence B).

IE Caused by Aerobic Gram-negative bacilli:

-Cardiac surgery is reasonable in combination with prolonged courses of combined antibiotic therapy for most patients with IE caused by non-HACEK Gram-negative aerobic bacilli, particularly *P aeruginosa* (Class IIb; Level of Evidence B).

-Combination antibiotic therapy with a β-lactam (penicillins, cephalosporins, or carbapenems) and either an aminoglycoside or fluoroquinolone for 6 weeks is reasonable (Class IIa; Level of Evidence C).

-Consultation with an infectious diseases expert in IE should be sought because of the various mechanisms of antibiotic resistance that can be found in the non- HACEK Gram-negative aerobic bacilli (Class I; Level of Evidence C).

-An evaluation of epidemiological factors, history of prior infections including cardiovascular infections, exposure to antimicrobials, clinical course, severity, and extracardiac sites of infection of the current infection should be performed in all culture-negative endocarditis cases (Class I; Level of Evidence C).

-Consultation with an infectious diseases specialist to define the most appropriate choice of therapy in patients with culture-negative endocarditis is recommended (Class I; Level of Evidence C).

-For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable (Class IIa; Level of Evidence C).

See appendix C for AHA guideline rating and full description of the Trustworthy Guideline grading system

Primary Literature:

The first review (Al-Omari 2014) includes a systematic study of oral antibiotic therapy for the treatment of infective endocarditis. Two clinical trials and eleven observational studies of the duration of antibiotic treatment was >2 weeks and oral antibiotics were the only antibiotics given after 2 weeks of treatment initiation. The two clinical trials included patients with intravenous drug use (n=98). The clinical trial comparing oral ciprofloxacin and rifampin versus conventional intravenous antibiotic therapy for uncomplicated right-sided *S. aureus* IE in intravenous drug users (IVDUs) reported cure rates of 89% and 90% in each arm, respectively (P =0.9); however, drug toxicities were more common in the latter group (62% versus 3%; P <0.01). The clinical trial comparing oral amoxicillin versus intravenous ceftriaxone for streptococcal IE reported 100% cure in both arms. Seven observational studies evaluating the use oral beta-lactams (five), oral ciprofloxacin in combination with rifampin (one), and linezolid (one) for the treatment of IE caused by susceptible bacteria reported cure rates between 77% and 100%. However, the two observational studies using aureomycin or sulfonamide had failure rates >75%.

The second review (Marti-Carvajal 2016) included is a Cochrane review of three antimicrobial clinical trials. The review found uncertain effects in terms of cure rates (9/28 (32.1%) with daptomycin versus 9/25 (36%) with low-dose gentamicin plus anti-staphylococcal penicillin or vancomycin, RR 0.89 95% CI 0.42 to 1.89; very low quality evidence). In participants receiving gentamycin plus glycopeptide only 13/23 (56%) were cured versus 11/11 (100%) receiving cloxacillin plus gentamicin (RR 0.59, 95% CI 0.40 to 0.85; very low quality evidence). No conclusive differences in terms of cure (15/34 (44%) with ceftriaxone plus gentamicin versus 21/33 (64%) with ceftriaxone alone, RR 0.69, 95% CI 0.44 to 1.10; very low quality evidence).

Summary of studies included in the systematic reviews

Al-Omari, Oral Antibiotic Therapy

Clinical Trials of Oral Antibiotics

Treatment	Duration	Micro Organism	Population	Cure rate
Oral ciprofloxacin and rifampin VS IV oxacillin or vancomycin (IV gentamicin for the first 5 days)	4 weeks	*MRSA, MSSA, CoNS*	85 IVDUs with right-side native valve infective endocarditis (NVIE) (40 in oral and 45 in IV arm)	90% oral vs 91% IV, p=0.9 Treatment toxicity: 3% oral vs 62% IV p<0.001
IV or IM ceftriaxone followed by high-dose oral amoxicillin vs IV or IM ceftriaxone	IV or IM ceftriaxone for 2 weeks with 2 weeks of oral amoxicillin vs 4 weeks of IV or IM ceftriaxone	*S. viridans, S. bovis*	13 IVDUs with right-side NVIE	100% in both arms, no reported treatment toxicity

Observational Studies

Treatment	Duration	Micro Organism	Population	Cure rate
IV vancomycin and oral linezolid	IV vancomycin 5.3± 3.4 days, oral linezolid 3 weeks	*MRSA, S.viridans, Enterococcus sp*.	12 NVIE, 2 PVIE	100%
IV ciprofloxacin and oral rifampin then oral ciprofloxacin and oral rifampin	IV ciprofloxacin + oral rifampin 1 week then oral ciprofloxacin and rifampin for 3 weeks	*S. aureus*	13 IVDUs with right-side NVIE	77%
High-dose Oral amoxicillin	6 weeks	*Streptococcus sp., Culture negative*	15 NVIE	87%
High-dose oral ampicillin with probenecid and then IM streptomycin	Oral ampicillin 6 weeks then 2 weeks of IM streptomycin	*S. viridans*	11 NVIE (left-sided)	90%
Oral ampicillin or propicillin	6 weeks	*S. viridans, E. faecalis, Culture Negative*	13 NVIE	92%
Oral phenithicillin	4-6 weeks	*S. viridans, E. faecalis, anaerobic bacteria*	10 NVIE	80%
Oral aureomycin	5-8 weeks	*S. viridans, E. faecalis, Culture Negative*	11 NVIE	36%
Oral sulfonamides	10 days-14 weeks	*Streptococcus sp., S.aureus, Enterococcus sp., H. influenza*	81 NVIE	10%

Marti-Carvajal, Antimicrobial Clinical Trials

Treatment	Duration	Micro Organism	Population	Cure rate
IV vancomycin or teicoplanin plus gentamicin versus IV cloxacillin plus gentamicin	2 weeks	*S. aureus*	34 NVIE	56% vancomycin or teicoplanin plus gentamicin versus 100% cloxacillin plus gentamicin
IV daptomycin versus low-dose gentamicin combined with either	4-6 weeks, mean 14-15 days	*S. aureus*	53 NVIE	32% with daptomycin versus 36% with low-dose gentamicin

anti-staphylococcal penicillins or vancomycin				plus anti-staphylococcal penicillin or vancomycin
IV ceftriaxone versus IV ceftriaxone with gentamicin	2- 4 weeks	*S. viridans or S. bovis*	67 NVIE	64% ceftriaxone vs 44% ceftriaxone with gentamicin

REFERENCES:

1. Al-Omari, A., et al. (2014). "Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review." BMC Infectious Diseases 14: 140.
2. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak, MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015; 132:1435–1486.
3. Marti Carvajal, A. J., et al. (2016). "A comparison of different antibiotic regimens for the treatment of infective endocarditis [Systematic Review]." Cochrane Database of Systematic Reviews 4: 4.

Appendix A. Search Strategy

Search Strategy:

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1 exp ENDOCARDITIS/dt [Drug Therapy] (4838)
2 exp ENDOCARDITIS/ (26920)
3 exp Anti-Bacterial Agents/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (319751)
4 2 and 3 (6194)
5 1 or 4 (7283)
6 exp Substance Abuse, Intravenous/ (14242)
7 exp Substance-Related Disorders/ (261276)
8 exp Administration, Intravenous/ (137734)
9 7 and 8 (2718)
10 (((iv or intraven* or inject*) adj5 (drug* or abus* or illicit* or addict* or (substanc* adj (use* or usag*)))) or ((needle* or syring*) adj5 (shar* or swap* or exchang* or borrow*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (49653)
11 6 or 9 or 10 (51638)
12 5 and 11 (274)
13 ((iv or intraven* or inject*) adj5 (drug* or abus* or illicit* or addict* or (substanc* adj (use* or usag*))) adj10 (endocardit* or ((heart* or cardi* or myocard* or coronary or atria* or ventric* or valv* or mitral or tricuspid*) adj3 (infect* or bacter* or coloniz*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (442)
14 ((iv or intraven* or inject*) adj5 (drug* or abus* or illicit* or addict* or (substanc* adj (use* or usag*))) adj10 (endocardit* or ((heart* or cardi* or myocard* or coronary or atria* or ventric* or valv* or mitral or tricuspid*) adj5 staph*))).mp. (431)
15 13 or 14 (446)
16 exp Anti-Bacterial Agents/ (660917)
17 dt.fs. (2059008)
18 16 or 17 (2496819)
19 15 and 18 (158)
20 12 or 19 (303)

Appendix B. Evidence Evaluation and GRADE criteria for rating a body of evidence on an intervention

PICO Question: In IV drug users with infective endocarditis (IE), what is the comparative clinical effectiveness of various anti-microbial therapies?					
Outcome: Cure Rate					
Overall Quality Rating…					
Low Quality Rating if: ☒ Studies inconsistent (wide variation of treatment effect across studies, population, interventions, or outcomes varied) ☐ Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome) ☒ Studies are imprecise (when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain) ☐ Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)		**Increase Quality Rating if:** ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect		**Quality (certainty) of evidence for studies as a whole:** ☐ High ☐ Moderate ☒ Low ☐ Very Low	
Study Acronym; Author; Year Published; Location	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Journal: *BMC Infectious Diseases* Author: Al-Omari, A., et al. Year Published: 2014 Location: Canada	**Aim**: To examine the literature on the efficacy of oral antibiotic therapy in the treatment of infective endocarditis **Study Type**: Systematic Review **Size**: 11 Studies	**Inclusion Criteria**: the duration of antibiotic treatment was >2 weeks and oral antibiotics where the only antibiotics given after 2 weeks of treatment initiation. To be eligible, studies had to a) report mortality and clinical cure as their outcomes of interest; b) report the microbiology of their IE cases; and c) present their data in a way that it allowed for the calculation of outcome rates as a function of the entire study cohort. **Exclusion Criteria**: Studies with a focus on culture negative endocarditis, case series	**Interventions** : *Observational studies:* oral beta-lactams, oral ciprofloxacin in combination with rifampin, and linezolid, aureomycin or sulfonamide *Clinical trials:* oral amoxicillin versus intravenous ceftriaxone; oral ciprofloxacin and rifampin versus conventional intravenous antibiotic therapy	**Results:** **Seven observational studies e**valuating the use oral beta-lactams (five), oral ciprofloxacin in combination with rifampin (one), and linezolid (one) for the treatment of IE caused by susceptible bacteria **reported cure rates between 77% and 100%.** **Two other observational studies using aureomycin or sulfonamide, however, had failure rates >75%.** **One clinical trial comparing oral amoxicillin versus intravenous ceftriaxone for streptococcal IE reported 100% cure in both arms.**	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

		(defined as studies with <10 participants) and articles without original data.		**The clinical trial comparing oral ciprofloxacin and rifampin versus conventional intravenous antibiotic therapy for uncomplicated right-sided S. aureus IE in intravenous drug users (IVDUs) reported cure rates of 89% and 90% in each arm, respectively (P =0.9); however, drug toxicities were more common in the latter group (62% versus 3%; P <0.01).**	
Journal: *Cochrane Database of Systematic Reviews* Author: Marti Carvajal, A. J., et al. Year Published: 2016 Location: Venezuela	**Aim**: To assess the existing evidence about the clinical benefits and harms of different antibiotics regimens used to treat people with infective endocarditis. **Study Type**: Systematic Review **Size**: Four RCTs involving 728 allocated/224 analyzed participants	**Inclusion Criteria**: randomized controlled trials assessing the effects of antibiotic regimens for treating possible infective endocarditis diagnosed according to modified Duke's criteria. Outcomes included: all-cause mortality, cure rates and adverse events **Exclusion Criteria**: people with possible infective endocarditis and pregnant women.	**Interventions** : levofloxacin plus standard treatment (anti-staphylococcal penicillin (cloxacillin or dicloxacillin), aminoglycoside (tobramycin or netilmicin) and rifampicin) versus standard treatment daptomycin versus low-dose gentamicin plus an anti-staphylococcal penicillin (nafcillin, oxacillin or flucloxacillin) or vancomycin cloxacillin plus gentamicin with a glycopeptide (vancomycin or teicoplanin) plus gentamicin ceftriaxone plus gentamicin versus ceftriaxone alone	**Results:** **Uncertain effects on all-cause mortality (8/31 (26%) with levofloxacin plus standard treatment versus 9/39 (23%) with standard treatment alone;** RR 1.12, 95% CI 0.49 to 2.56, very low quality evidence). **Uncertain effects in terms of cure rates (9/28 (32.1%) with daptomycin versus 9/25 (36%) with low-dose gentamicin plus anti-staphylococcal penicillin or vancomycin,** RR 0.89 95% CI 0.42 to 1.89; very low quality evidence). **In participants receiving gentamycin plus glycopeptide only 13/23 (56%) were cured versus 11/11 (100%) receiving cloxacillin plus gentamicin** (RR 0.59, 95% CI 0.40 to 0.85; very low quality evidence). **No conclusive differences in terms of cure (15/34 (44%) with ceftriaxone plus gentamicin versus 21/33 (64%) with ceftriaxone alone,** RR 0.69, 95% CI 0.44 to 1.10; very low quality evidence).	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

References:

Al-Omari, A., et al. (2014). "Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review." BMC Infectious Diseases 14: 140.
Marti Carvajal, A. J., et al. (2016). "A comparison of different antibiotic regimens for the treatment of infective endocarditis [Systematic Review]." Cochrane Database of Systematic Reviews 4: 4.

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix C. Trustworthy Guideline rating scale and Guideline Rating

Guideline Rating

Guideline Issuer	American Heart Association 2015
1. Transparency	A
2. Conflict of interest	A
3. Development group	A
4. Systematic Review	B
5. Supporting evidence	A
6. Recommendations	A
7. External Review	NR
8. Currency and updates	B

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.

C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.

C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated