Quality of Critical Care Clinical Practice Guidelines Involving Pharmacotherapy Recommendations

ABSTRACT

Purpose: To assess the quality of critical care clinical practice guidelines (CPGs) involving pharmacotherapy recommendations.

Methods: A systematic electronic search was performed using PubMed, Medline, and Embase for critical care CPGs published between 2012-2022 and involving pharmacotherapy recommendations. The Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument was employed to appraise CPG quality with independent assessment by two appraisers.

Results: Twenty-one CPGs were evaluated. The number of recommendations in each guideline ranged from 2 to 250 with a total of 1604 recommendations. The number of strong (vs. weak) recommendations in each guideline ranged from 0-31 with a total of 116 strong recommendations, or 7.23% of total recommendations. There was at least one pharmacist author in 9 (43%) of guidelines. The domains with highest quality scores were scope and purpose (0.88, 95%CI 0.85-0.92), rigor of development (0.80, 95CI 0.77-0.83), clarity of presentation (0.84, 95%CI 0.81-0.87), and editorial independence (0.86, 95%CI 0.79-0.94), while those with the lowest scores were stakeholder involvement (0.69, 95%CI 0.63-0.75) and applicability (0.49, 95%CI 0.43-0.55). Involvement of a pharmacist in CPGs was associated with significantly higher scoring for stakeholder involvement (P=0.0356).

Conclusion: Strong recommendations account for less than 10% of the recommendations in CPGs. However, there remain concerns related to applicability (i.e. advice or tools for putting recommendations into practice) and stakeholder involvement (i.e. individuals from all relevant groups). It is important to involve pharmacists in CPGs with pharmacotherapy recommendations.

INTRODUCTION

Clinical practice guidelines (CPGs) are valuable tools that provide clinicians with recommendations for informed decision-making based on the best available evidence. However, research indicates that clinicians frequently do not apply the recommendations from CPGs to the patient care setting. Approximately 30-40% of patients do not receive treatment based on evidence-based recommendations from CPGs.[1]

In some cases, clinicians do not follow recommendations in CPGs (particularly those based on low levels of evidence with weak recommendations) because of patient-specific issues that preclude following guideline recommendations, or suggest another more personalized approach is preferable. One factor contributing to the lack of utilization of CPGs relates to the quality of the evidence base supporting the recommendations. This is particularly a problem when prescribing medications in the intensive care unit (ICU) setting, since there is a paucity of high-level evidence upon which to base clinical decisions. In one evaluation of pharmacotherapy recommendations in CPGs published in 2010, only one-third of strong recommendations were deemed supportable by high-level evidence.[2]

There are ongoing attempts to standardize the approaches for grading quality of evidence, proposing strengths of recommendations, and evaluating the processes of guideline development. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system is a standardized, systematic approach for grading quality of evidence with subsequent recommendations classified as strong or weak.[2] The Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument is an international standard that addresses the processes of clinical practice guideline development such as rigor and transparency that can lead to variability in the quality of guidelines.[4] The AGREE II instrument evaluates these variables to understand the impact they have on the quality of CPGs. The purpose of this study was to evaluate the quality of CPGs involving critical care pharmacotherapy recommendations with particular focus on the number of strong recommendations in the guidelines. We also investigated potential associations between scaled domain scores using the AGREE II instrument and factors such as pharmacist involvement in guideline development, year of publication, and number of guideline recommendations.

METHODS

A search for CPGs involving critical care pharmacotherapy was conducted with the assistance of a health sciences librarian with expertise using PubMed, Medline, and Embase. The results were reviewed by two experienced critical care clinicians and relevant guidelines were identified with the intent of including only those guidelines involving pharmacotherapy that were published in the last ten years (1/1/2012 to 1/1/2022). The initial search using the terms This study did not involve data from human participants.

The data collection form included guideline name, year published, number of authors, number of pharmacist authors, number of recommendations, number of strong recommendations (in contrast to weak recommendations as promulgated by the guideline panels based on the available evidence), and scaled AGREE II domain scores. The AGREE II instrument is formulated to assess 23 aspects of quality within 6 quality domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence). The rating of items in AGREE II range from 1 (strongly disagree) to 7 (strongly agree). The guidelines were evaluated and scored by two independent researchers using the AGREE II tool. A third researcher independently evaluated approximately 14% of the included guidelines to ensure appropriate application of the AGREE II tool. The scaled AGREE II domain scores were calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score of that domain.[5] Since the scaled AGREE II score takes into consideration all evaluator scores, adjudication of discrepancies between the two independent reviewers to reach consensus was not required.

Data was collected in Microsoft Excel (Microsoft Corporation, Redmond, WA) for initial analysis with subsequent testing using STATA® 13.1, College Station, TX. Potential associations were evaluated between the independent variables of number of pharmacists involved as authors, year of publication, and number of recommendations, and the dependent variable of each of the 6 scaled AGREE II scores using simple linear regression with subsequent input into multiple regression models for variables with p-values less than 0.2. Regression diagnostics included statistical graphics, testing for non-normality (Shapiro-Wilk W test) and heteroscedasticity (Cook-Weisberg test). Additionally, the Wilcoxon rank-sum test was used to assess domain scores with or without pharmacist involvement. Significance for all testing was defined as alpha less than 0.05.

RESULTS

Twenty-one guidelines involving 412 total authors were included in this evaluation (Table 1).[6-26] The number of recommendations in each guideline ranged from 2 to 250 with a total of 1604 recommendations. The number of strong recommendations in each guideline ranged from 0 to 31 with a total of 116 strong recommendations, or 7.23% of the total number of recommendations. There was at least one pharmacist author in 9 (43%) of the guidelines. The results of CPG quality using domain score evaluations are shown in Table 2. In the regression analysis, the only significant associations were publication year (i.e. more recent publication) for domain 2 (stakeholder involvement) (coefficient: 0.02056, 95% CI 0.0019 to 0.0493) and total number of recommendations (i.e. increasing number) for domain 4 (clarity of presentation) (coefficient: 0.0005, 95% CI 0.0006 to 0.0009). Involvement of a pharmacist in CPGs was associated with significantly higher scoring for domain 2 (P=0.0356), but not with other domains.

DISCUSSION

The primary finding of this study is that despite for an increasing number CPGs involving critical care pharmacotherapy, there remains substantial room for improvement in the quality of the guidelines, and particularly the evidence serving as the basis for recommendations in the guidelines as exemplified by the small number of strong recommendations, 7.23% of the total. Additionally, although all of the guidelines under evaluation had at least one recommendation related to pharmacotherapy, only 43% of the guidelines had at least one pharmacist as an author. The quality score was significantly higher (P=0.0356) for domain 2 (stakeholder involvement) when at least one pharmacist was an author of CPGs.

Our findings somewhat contrast to the results of a previous study evaluating critical care guidelines by Chen et al, which also assessed quality using the AGREE II instrument.[5] In the study by Chen et al., there were 54% strong recommendations compared to the 7.23% in our study, a discrepancy likely due to differences in the number and type of CPGs under review, dates of guideline inclusion, and factors such as rigor of guideline development. Chen et al. evaluated 89 CPGs compared to 21 in our study, but they did not limit their assessment to guidelines involving pharmacotherapy, nor did they limit by year of study inclusion (i.e., literature search from inception to 2017 vs. 2012 to 2022, respectively). Therefore, the total number of recommendations in the study by Chen et al. was much larger than in ours (3125 vs. 1604, respectively). While the quality of guidelines based on three calculated domain scores was similar (i.e. difference in score within 0.05) in the study by Chen et al. and ours for domains 1 (scope and purpose), 4 (clarity of presentation), and 5 (applicability) (0.93 vs. 0.88, 0.83 vs. 0.84 for 4, 0.5 vs. 0.49, respectively), the differences were more substantial for domains 2 (stakeholder involvement), 3 (rigor of development), and 6 (editorial independence) (0.37 vs. 0.69, 0.59 vs. 0.80, and 0.67 vs. 0.86, respectively). For the latter three domains with substantial rating differences, all demonstrated improvement in our more recent evaluation, which is consistent with increasing standardization (e.g. use of GRADE).

In the Chen et al. investigation, no significant associations were found between year of publication and any of the six scaled domain scores using regression analysis, while we found one statistically significant association and that was between year of publication and domain 2 (stakeholder involvement) with more recent CPGs demonstrating increasing stakeholder involvement. Additionally, we found a statistically significant association between the total number of recommendations in CPGs and domain 4 (clarity of presentation) (coefficient: 0.0005, 95% CI 0.0006 to 0.0009), but these results seem unlikely to be clinically meaningful. Chen et al. found the number of participating societies was associated with significant domain score improvement in domains 2 (P=0.033), 3 (P=0.027), 4 (P=0.029), and 5 (P=0.023), although what constituted a “society” was not clearly defined. We did not evaluate potential associations between number of sponsoring organizations and domain scores, since there was typically only one or two professional societies involved in CPG development.

There is one previous assessment of critical care CPGs by Gorman et al. that was similar to our evaluation in that the focus was on guidelines involving pharmacotherapy and a similar number of CPGs were evaluated (24 vs. 21, respectively).[2] However, there are also important differences between the assessment of Gorman et al. and our evaluation, such as the years of study inclusion (1966-2008 vs. 2012-2022, respectively) and use of different versions of the AGREE instrument (I vs. II, respectively). At the time of publication in 2010, the findings by Gorman et al. were important since they found high quality evidence supporting only 36% of strong CPG recommendations.

When comparing our findings to those of Chen et al.,[5] our findings suggest that the quality of CPGs continues to improve over time based on rigor of development (0.59 vs. 0..8, respectively) using the AGREE II instrument recognizing the limitations related to different CPGs and scoring assessments. However, there are two domains in particular need of future focus by CPG development teams. Those domains concern applicability (i.e. advice or tools for putting the recommendations into practice) and stakeholder involvement (i.e. individuals from all relevant groups). With respect to stakeholder involvement, including pharmacists in CPG development would be beneficial in helping to ensure that all relevant professional groups and experiences are available when formulating recommendations. Arguments in favor of pharmacist involvement in CPG development are particularly strong when the guidelines have recommendations pertaining to pharmacotherapy, since pharmacists have expertise in medication optimization.

There were several limitations to this study. In particular, the assessment of quality using the AGREE II instrument has reliability concerns due to the somewhat inherent subjectivity related to scoring and the involvement of two reviewers (some other investigations have 3 or 4).

However, there was a discussion to reach mutual consensus between evaluators for ambiguous items and the AGREE II instrument itself incorporates a scaled score to account for appraiser variance. Additionally, the domain scores in our study were similar for 3 of the domains and higher for the other 3 domains compared to a previous study assessing the quality of CPGs, which suggests ongoing improvement in CPG development as expected with increasing attention to guideline standardization using the GRADE system.

CONCLUSION

Strong recommendations account for less than 10% of the recommendations in CPGs. However, there are two domains in particular need of future focus by CPG development teams. Those domains concern applicability (i.e. advice or tools for putting the recommendations into practice) and stakeholder involvement (i.e. individuals from all relevant groups). With respect to stakeholder involvement, there is good reason to involve pharmacists as medication experts in CPG development, particularly for those CPGs concerning pharmacotherapy.

REFERENCES

1. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. *Healthcare (Basel)*. 2016 Jun 29;4(3):36. doi: 10.3390/healthcare4030036. PMID: 27417624; PMCID: PMC5041037.
2. Gorman SK, Chung MH, Slavik RS, Zed PJ, Wilbur K, Dhingra VK. A critical appraisal of the quality of critical care pharmacotherapy clinical practice guidelines and their strength of recommendations. *Intensive Care Med*. 2010 Oct;36(10):1636-43. doi: 10.1007/s00134-010-1786-8. Epub 2010 Mar 9. Erratum in: *Intensive Care Med*. 2010 Oct;36(10):1798-1801. PMID: 20217048.
3. Diekemper RL, Patel S, Mette SA, Ornelas J, Ouellette DR, Casey KR. Making the GRADE: CHEST Updates Its Methodology. *Chest.* 2018 Mar;153(3):756-759. doi: 10.1016/j.chest.2016.04.018. Epub 2016 Apr 30. PMID: 27142185.
4. AGREE: Advancing the science of practice guidelines. AGREE II. https://www.agreetrust.org/resource-centre/agree-ii/ (Accessed January 31, 2022).
5. Chen Z, Hong Y, Liu N, Zhang Z. Quality of critical care clinical practice guidelines: assessment with AGREE II instrument. *J Clin Anesth.* 2018;51:40-47. doi: 10.1016/j.jclinane.2018.08.011. Epub 2018 Aug 7. PMID: 30092459.
6. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y. Epub 2021 Oct 2. PMID: 34599691; PMCID: PMC8486643.

7. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, Fourth Edition. *Neurosurgery*. 2017 Jan 1;80(1):6-15. doi: 10.1227/NEU.0000000000001432. PMID: 27654000.
8. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018 Sep;46(9):e825-e873. doi: 10.1097/CCM.0000000000003299. PMID: 30113379.
9. Panchal AR, Bartos JA, Cabañas JG, et al; Adult Basic and Advanced Life Support Writing Group. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2020 Oct 20;142(16_suppl_2):S366-S468. doi: 10.1161/CIR.0000000000000916. Epub 2020 Oct 21. PMID: 33081529.
10. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019 Oct 1;200(7):e45-e67. doi: 10.1164/rccm.201908-1581ST. PMID: 31573350; PMCID: PMC6812437.
11. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: A statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46. doi: 10.1007/s12028-015-0222-x. PMID: 26714677.
12. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious

Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016 Sep 1;63(5):e61-e111. doi: 10.1093/cid/ciw353. Epub 2016 Jul 14. Erratum in: Clin Infect Dis. 2017 May 1;64(9):1298. Erratum in: *Clin Infect Dis*. 2017 Oct 15;65(8):1435. Erratum in: *Clin Infect Dis*. 2017 Nov 29;65(12):2161. PMID: 27418577; PMCID: PMC4981759.

13. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. *Neurosurgery*. 2013 Mar;72 Suppl 2:93-105. doi: 10.1227/NEU.0b013e31827765c6. PMID: 23417182.
14. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of venous thrombosis in neurocritical care patients: An evidence-based guideline: a statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care*. 2016 Feb;24(1):47-60. doi: 10.1007/s12028-015-0221-y. PMID: 26646118.
15. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2016 Nov;44(11):2079-2103. doi: 10.1097/CCM.0000000000002027. PMID: 27755068.
16. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: Treatment of convulsive status epilepticus in children and adults: Report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr*. 2016 Jan-Feb;16(1):48-61. doi: 10.5698/1535-7597-16.1.48. PMID: 26900382; PMCID: PMC4749120.
17. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-st-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014 Dec 23;64(24):e139-e228. doi:

10.1016/j.jacc.2014.09.017. Epub 2014 Sep 23. Erratum in: J Am Coll Cardiol. 2014 Dec 23;64(24):2713-4. Dosage error in article text. PMID: 25260718.

18. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE Disease: CHEST guideline and expert panel report. *Chest*. 2016 Feb;149(2):315-352. doi: 10.1016/j.chest.2015.11.026. Epub 2016 Jan 7. Erratum in: *Chest*. 2016 Oct;150(4):988. PMID: 26867832.
19. McClave SA, Taylor BE, Martindale RG, et al. Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016 Feb;40(2):159-211. doi: 10.1177/0148607115621863. Erratum in: *JPEN J Parenter Enteral Nutr*. 2016 Nov;40(8):1200. PMID: 26773077.
20. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017 Mar 15;64(6):e34-e65. doi: 10.1093/cid/ciw861. PMID: 28203777; PMCID: PMC5848239.
21. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-84. doi: 10.1159/000339789. Epub 2012 Aug 7. PMID: 22890468.
22. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the

American Heart Association/American Stroke Association. *Stroke*. 2019 Dec;50(12):e344-e418. doi: 10.1161/STR.0000000000000211. Epub 2019 Oct 30. Erratum in: *Stroke*. 2019 Dec;50(12):e440-e441. PMID: 31662037.

23. Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017 May 1;195(9):1253-1263. doi: 10.1164/rccm.201703-0548ST. Erratum in: *Am J Respir Crit Care Med*. 2017 Jun 1;195(11):1540. PMID: 28459336.
24. Nanchal R, Subramanian R, Karvellas CJ, et al. Guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU: Cardiovascular, endocrine, hematologic, pulmonary, and renal considerations. *Crit Care Med*. 2020 Mar;48(3):e173-e191. doi: 10.1097/CCM.0000000000004192. PMID: 32058387.
25. Kane-Gill SL, Dasta JF, Buckley MS, et al. Clinical practice guideline: Safe medication use in the ICU. *Crit Care Med*. 2017 Sep;45(9):e877-e915. doi: 10.1097/CCM.0000000000002533. PMID: 28816851.
26. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 Jan 29;127(4):e362-425. doi:

10.1161/CIR.0b013e3182742cf6. Epub 2012 Dec 17. Erratum in: *Circulation*. 2013 Dec 24;128(25):e481. PMID: 23247304.

Key Points

1. Clinicians frequently do not follow the recommendations in clinical practice guidelines, which in some cases may be due to the low quality of evidence supporting the recommendations.
2. Strong recommendations account for less than 10% of recommendations in guidelines pertaining to critical care.
3. There is good reason to involve pharmacists as medication experts in guideline development, particularly for those CPGs concerning pharmacotherapy.

Key Words: critical care; clinical practice guidelines; quality; pharmacy; pharmacotherapy, medication

Table 1. List of clinical practice guidelines undergoing evaluation.

Reference	Guideline
6	Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021
7	Guidelines for the Management of Severe Traumatic Brain Injury
8	Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adults Patients in the ICU
9	2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care
10	Diagnosis and Treatment of Adults with Community-acquired Pneumonia
11	Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage
12	Management of Adults with Hospital-acquired and Ventilator-associated pneumonia
13	Pharmacological Therapy for Acute Spinal Cord Injury
14	Prophylaxis of Venous Thrombosis in Neurocritical Care Patients
15	Sustained Neuromuscular Blockade in the Adult Critically Ill Patients
16	Status Treatment of Convulsive Status Epilepticus in Children and Adults
17	2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes
18	Antithrombotic Therapy for VTE Disease
19	Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

20	2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis
21	KDIGO Clinical Practice Guideline for Acute Kidney Injury
22	Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke
23	An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome
24	Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations
25	Clinical Practice Guideline: Safe Medication Use in the ICU
26	Guideline for the Management of ST-Elevation Myocardial Infraction

Table 2. Domain score calculations for the critical care pharmacotherapy guidelines.

Domain		Mean	Standard Error	95% CI*
1	Scope and purpose	0.88	0.02	0.85 to 0.92
2	Stakeholder involvement	0.69	0.03	0.63 to 0.75
3	Rigor of development	0.80	0.02	0.77 to 0.83
4	Clarity of presentation	0.84	0.02	0.81 to 0.87
5	Applicability	0.49	0.26	0.43 to 0.55
6	Editorial independence	0.86	0.04	0.79 to 0.94

*CI, confidence interval