Original Article

A quality assessment of evidence-based guidelines for the prevention and management of ventilator-associated pneumonia: a systematic review

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Background: Numerous evidence-based guidelines (EBGs) pertaining to ventilator-associated pneumonia (VAP) have been published by domestic and international organizations, but their qualities have not been reported.

Methods: A systematic search of the literature was performed up to July 2018 for relevant guidelines. Guidelines were eligible for inclusion if they incorporated recommendation statements for prevention and/or management in adults or children with VAP and were developed on a systematic evidence-based method. Four reviewers evaluated each guideline using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, which comprises 23 items organized into six domains in addition to two overall items.

Results: Thirteen EBGs were identified for review. An overall high degree of agreement among reviewers was reached [intra-class correlation coefficient (ICC), 0.885; 95% CI, 0.862–0.905] during their review. The scores (mean, range) for the six AGREE domains were: *scope and purpose* (61%, 51–74%), *stakeholder involvement* (36%, 18–68%), *rigor of development* (41%, 22–59%), *clarity and presentation* (56%, 47–71%), *applicability* (38%, 21–59%) *and editorial independence* (50%, 0–77%). Only two EBGs (15.4%) were rated "recommended" for clinical practice. Approximately 86% of recommendations were based on moderate or low levels of evidence (levels B–D were 46.2%, 19.0%, and 21.2%, respectively). The recommendations for prevention and management of VAP were similar among the different EBGs.

Conclusions: The overall quality of the identified EBGs pertaining to VAP was classified as moderate. The management of VAP varied by guideline. More high-quality evidence is needed to improve guideline recommendations.

Keywords: Evidence-based guidelines (EBGs); ventilator-associated pneumonia (VAP); quality assessment; AGREE II; review

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Introduction

Ventilator-associated pneumonia (VAP) is the most common type of hospital-acquired infection with a high incidence (2.5–40%) and mortality (13–25.2%), which increase in patients with a multi-drug resistant or pan-drug resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or *methicillin-resistant Staphylococcus aureus* (1,2). Patients with VAP require long hospitalization times and incur high costs of hospitalization (3-5). In China, the incidence and mortality of VAP are 4.7–55.8% and 19.4–51.6%, respectively, significantly higher than in Western countries (3,6). The prevention and management of VAP remains a major challenge to clinicians, despite advances in critical medicine care, improved mechanical ventilation, and the widespread use of antibacterial drugs (1). Evidence-based guidelines (EBGs) for VAP are needed for the best clinical decision (7,8).

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument is an internationally recognized and reliable method of assessing guidelines (9-11). We believe that it is necessary to conduct a systematic literature search to identify existing EBGs pertaining to VAP, as well as evaluate these guidelines' methodological quality and differences in EBGs obtained from different sources.

Methods

Literature search

A literature search was conducted in the PubMed, Excerpt Medical Database (EMbase), Web of Science, Cochrane Library, WANFANG database, Chinese National Knowledge Infrastructure (CNKI), VIP information, Chinese Biomedical Literature database (CBM), U.S National Guideline Clearinghouse (NGC), Guidelines-International Network (G-I-N), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group (NZGG), National Health and Medical Research Council (NHMRC), American College of Chest Physicians (ACCP), European Respiratory Society (ERS), and British Thoracic Society (BTS) to identify EBGs for VAP. The search strategy used combinations of the following key words: "ventilator-associated pneumonia", "VAP", "hospital acquired pneumonia", "HAP", "nosocomial pneumonia", "guideline", "guidance", "guide", "recommendation", "consensus", "suggestion", "strategy" and "strategies". The search results were limited to guidelines focusing on the prevention and/or management in adults or children with VAP and with the publication dates from database inception to July 2018.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (I) EBGs—this refers to a guideline providing clear evidence-supported recommendations for clinical practice that includes the strength of recommendation or level of evidence identified by a systematic search and assessment of current evidence; (II) VAP; (III) interventions for the prevention and/or management of VAP; (IV) Chinese or English publications.

Exclusion criteria were as follows: (I) old versions or duplication of guidelines; (II) translated or adapted versions of guidelines from other countries; (III) systematic reviews or interpretations of guidelines; (IV) clinical trials; (V) guidelines published in books, booklets, or government documents; (VII) publications not in Chinese or English.

Guidelines selection and data extraction

Two pairs of reviewers (K Wan and G Yan) and (B Zou and C Huang) independently assessed the title and abstracts of publications found using the search criteria. Full-text manuscripts were reviewed when these suggested the publication met inclusion criteria. Studies included from a reference and citation analysis were also assessed.

The two pairs of reviewers extracted general characteristics of the included EBGs. The following descriptive information was extracted from each guideline: year of publication, version, country of guideline development, institution or organization responsible for guideline development, target population, number of references, recommendations for prevention and/or management, strength of recommendation, level of evidence, and size of the document. A cross-check of the assessment results and descriptive information was performed. Any disagreement was resolved by discussion or by consulting a third expert (M Jiang).

Quality assessment

The AGREE II instrument is the most highly validated and had the most extensive coverage over domains to assess the methodological quality of guidelines (12). This standard is widely recognized for its utility by international organizations, including the World Health Organization

(WHO). The instrument contains 23 specific items divided into six domains, followed by two overall items (11). The six domains are: *scope and purpose* (3 items), *stakeholder involvement* (3 items), *rigor of development* (8 items), *clarity and presentation* (3 items), *applicability* (4 items) and *editorial independence* (2 items). Each item is scored using a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree), based on examples and instructions described in the AGREE II manual (11). The standardized score for the individual domain ranges from 0% to 100%. This score is calculated using the formula: (obtained score – minimal possible score)/(maximal possible score – minimal possible score) × 100% (11).

The final overall guideline recommendation considered all domain items (9). The AGREE II manual (11) does not provide guidance for rating the overall quality for each guideline and evaluating the final recommendation for use. Considering the importance and significance of these two domains, we assigned double weight to rigor of development and applicability (9,13). A guideline was "recommended" if overall scores were above 60%, "recommended with modifications" if scores were between 30% and 60%, and "not recommended" if scores were below 30% (9). All reviewers were trained in AGREE II scoring to ensure that each individual's understanding of each item was basically the same. Four well-trained reviewers (Drs. K Wan, G Yan, B Zou, and C Huang) assessed the guidelines independently using the AGREE II instrument.

Statistical analysis

The overall assessment of conformity between reviewers across each domain was calculated using the intra-class correlation coefficient (ICC) with 95% CIs (14). ICC that was 0.75 or higher was interpreted as excellent reliability, 0.40 to 0.75 as moderate reliability and less than 0.40 as poor reliability (15-17). Descriptive and statistical analyses were conducted using SPSS version 23.0 (IBM Corporation). A P value <0.05 was considered statistically significant (18).

Results

Study selection and guidelines characteristics

A comprehensive search of databases and websites identified 2,081 studies. A total of 591 were duplicate studies and 1,377 more were excluded after screening titles and abstracts. The remaining 113 studies were screened by full text analysis. One hundred of these were excluded using study criteria. Thirteen unique EBGs were identified for evaluation (1,3,19-29) (*Figure 1* and *Table 1*). All guidelines were published from 2004 to 2018. Four (30.8%) were developed in Canada, two (15.4%) in the USA, two (15.4%) in China, and the rest in Japan, South Africa, India, United Kingdom and combinations of multiple countries. Three (23.1%) guidelines focused on treatment of disease, three (23.1%) on prevention, and the rest on both. Nine (69.2%) guidelines provided recommendations for adults with VAP, one (7.7%) for children, and two (15.4%) for both. Only three (23.1%) guidelines defined the specific age of patients they were meant for. Twelve (92.3%) guidelines were developed by medical societies or associations.

Quality assessment of guidelines

Overall agreement between reviewers was considered excellent (ICC, 0.885; 95% CI, 0.862–0.905).

Standardized AGREE II domain scores and overall assessment of the 13 guidelines are summarized in *Table 2*. The mean overall score for all included guidelines was moderate (mean ± SD, 45%±10%; range, 31–63%). The *scope and purpose* domain received the highest domain score (mean, 61%; range, 51–74%). *Clarity of presentation* had the second highest score (mean, 56%; range, 47–71%), and two (15.4%) domains had scores of less than 50%. *Editorial independence* had domain scores that varied widely among the guidelines (SD, 28%; range, 0–77%); the mean score was 50%. Two guidelines (15.4%) developed in China did not include information defining sponsorship information or conflicts of interest among development members. Guidelines scored relatively low in the *rigor of development* and *applicability* domains with a mean of 41% and 38%, respectively. Only seven (53.8%) guidelines detailed the search strategies used to obtain clinical evidence and six (46.2%) described methods to be used to update the guidelines in the future. Three (23.1%) guidelines analyzed obstacles identified in applying the guidelines. The *stakeholder involvement* domain received the lowest mean score with a mean of 36%. Six (46.2%) guidelines had a score less than 30% in this domain. No guideline stated that patients or the general public were included in the development group.

Among the 13 including EBGs, two (15.4%) were "recommended" for clinical practice, achieving high

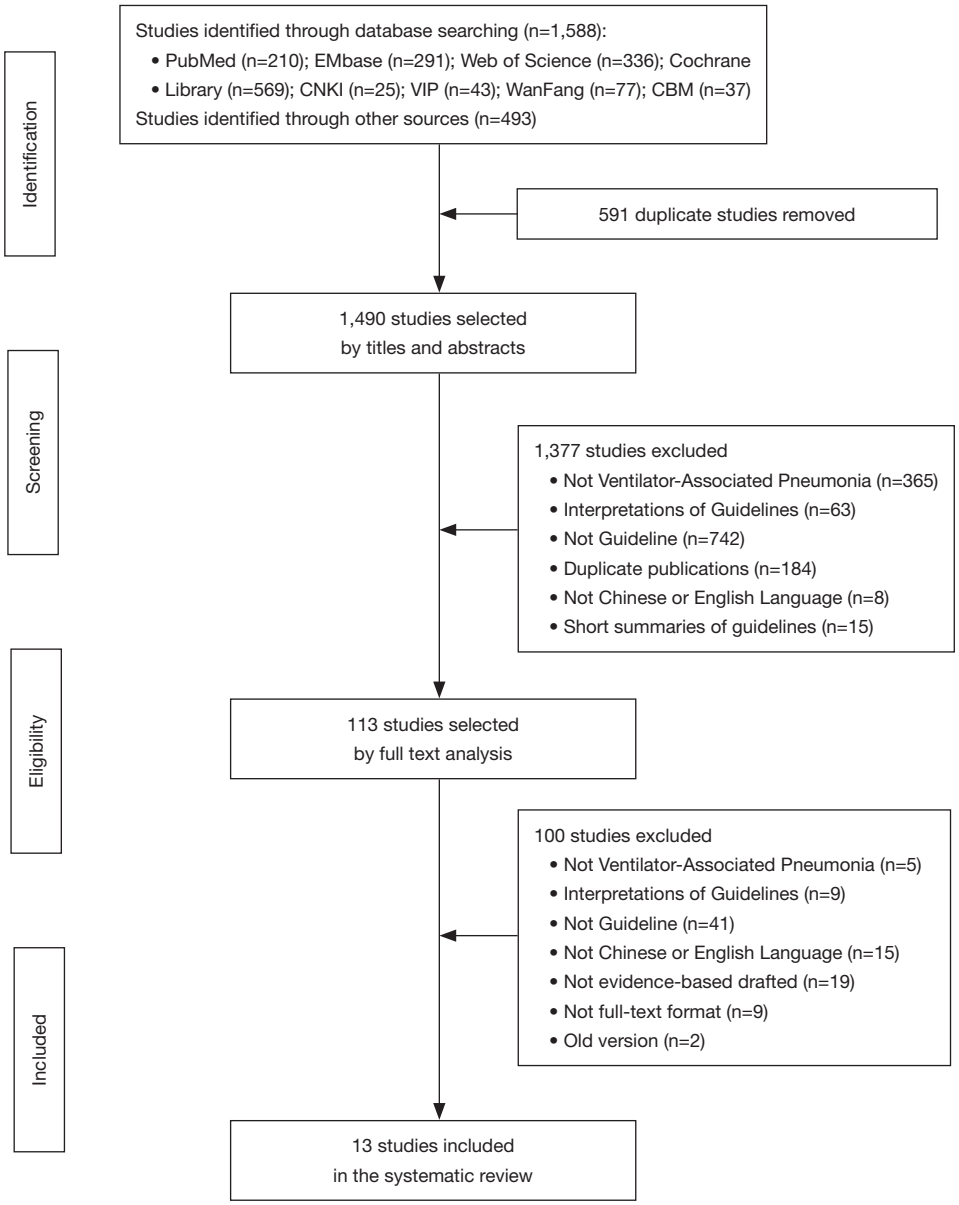

Figure 1 A flowchart of guidelines searching and selection.

overall scores above 60%, and the remaining (84.6%) were "recommended with modifications", scoring of 30–60% (*Table 2*). No guidelines were "not recommended".

Grading systems used to develop evidence and recommendations for guidelines

Guideline developers used different systems assess the evidence presented in the different EBGs pertaining to VAP (*Table 1*). Six (46.2%) of the 13 guidelines used the Grades of Recommendations Assessment, Development and Evaluation (GRADE) approach, four (30.8%) used the Canadian Task Force on the Periodic Health Examination (CTHPHC) system, one (7.7%) used the Scottish Intercollegiate Guidelines Network (SIGN) system, and two (15.4%) used a self-formulated system. We developed a new system based on the GRADE approach (see *Table S1*) (13,30). In this new system we re-classified the levels of evidence and the strength of recommendations of included EBGs.

Table 1 Characteristics of the included VAP guidelines

Title	Guideline	Origin	Institution/development group	Topic (s) addressed	Patient population	Focus of guideline	Grading system	Number of references
Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia	Dodek 2004 (19)	Canada	CCCS and CCCTG	VAP	Adults	Prevention	Self-formulated	107
Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment	Muscedere 2008a (20)	Canada	Expert Committee and CCCTG	VAP	Adults	Treatment	CTFPHE	80
Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention	Muscedere 2008b (21)	Canada	Expert Committee and CCCTG	VAP	Adults	Prevention	CTFPHE	109
Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British society for antimicrobial chemotherapy	Masterton 2008 (22)	United Kingdom	BSAC	VAP/HAP	Adults (≥16 y)	Treatment; prevention	SIGN	333
Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults	Rotstein 2008 (23)	Canada	AMM; IDC and CTS[1]	VAP/HAP	Adults	Treatment; prevention	CTFPHE	381
Guideline for the diagnosis, prevention and treatment of paediatric ventilator-associated pneumonia	Morrow 2009 (24)	South Africa	Expert Committee	VAP	Children (<12 y)	Treatment; prevention	ACCP	120
Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults: joint ICS/NCCP(I) recommendations	Gupta 2012 (25)	India	ICS and NCCP	VAP/HAP	Adults	Treatment; prevention	GRADE	451
Guidelines for the diagnosis, prevention and treatment of ventilator-associated pneumonia	Li 2013 (3)	China	CSCCM	VAP	No declared	Treatment; prevention	GRADE	341
Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update	Klompas 2014 (26)	America	SHEA	VAP	Both	Prevention	GRADE	241
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	Kalil 2016 (27)	America	IDSA and ATS	VAP/HAP	Adults	Treatment	GRADE	364

Table 1 (*continued*)

Table 1 (*continued*)

Title	Guideline	Origin	Institution/development group	Topic (s) addressed	Patient population	Focus of guideline	Grading system	Number of references
JAID/JSC guidelines for the treatment of respiratory infectious diseases: the Japanese Association for Infectious Diseases/ Japanese Society of Chemotherapy—The JAID/JSC Guide to Clinical Management of Infectious Disease/Guideline-preparing Committee Respiratory Infectious Disease WG	Mikasa 2016 (28)	Japan	JAID and JSC	VAP/HAP	Children[a]	Treatment	GRADE	413
International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia	Torres 2017 (29)	Europe, Latin America	ERS; ESICM; ESCMID and ALAT	VAP/HAP	Adults	Treatment; prevention	GRADE	133
Guidelines for the diagnosis and treatment of hospitals -acquired pneumonia and ventilator-associated pneumonia in adults in China	Qu 2018 (1)	China	CTS[2]	VAP/HAP	Adults (≥18 y)	Treatment; prevention	Self-formulated	302

[a], VAP were not discussed separately and specifically in the section of adults. CCCS, Canadian Critical Care Society; CCCTG, Canadian Critical Care Trials Group; BSAC, British Society of Antimicrobial Chemotherapy; AMM, Association of Medical Microbiology; IDC, Infectious Disease Canada; CTS[1], Canadian Thoracic Society; ICS, Indian Chest Society; NCCP, National College of Chest Physicians; CSCCM, Chinese Society of Critical Care Medicine; SHEA, Society for Healthcare Epidemiology of America; IDSA, Infectious Diseases Society of America; ATS, American Thoracic Society; JAID, Japanese Association for Infectious Diseases; JSC, Japanese Society of Chemotherapy; ERS, European Respiratory Society; ESICM, European Society of Intensive Care Medicine; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ALAT, Asociación Latinoamericana del Tórax; CTS[2], Chinese Thoracic Society; CTFPHE, Canadian Task Force on the Periodic Health Examination; SIGN, Scottish Intercollegiate Guidelines Network; ACCP, American College of Clinical Pharmacy; GRADE, Grading of Recommendations assessment, Development and Evaluation. VAP, ventilator-associated pneumonia.

Table 2 AGREE II domain scores and overall assessment of the included VAP guidelines

Guideline	Score of the Six AGREE II Domains (%)						Overall assessment
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence	
Dodek 2004 (19)	51	42	52	54	39	77	Recommended with modification
Muscedere 2008a (20)	60	40	53	53	45	77	Recommended with modification
Muscedere 2008b (21)	60	40	52	54	45	77	Recommended with modification
Masterton 2008 (22)	58	26	36	47	28	65	Recommended with modification
Rotstein 2008 (23)	58	21	31	57	35	42	Recommended with modification
Morrow 2009 (24)	63	25	22	56	25	29	Recommended with modification
Gupta 2012 (25)	58	26	39	57	40	38	Recommended with modification
Li 2013 (3)	54	18	52	57	26	0	Recommended with modification
Klompas 2014 (26)	58	28	23	47	30	67	Recommended with modification
Kalil 2016 (27)	71	68	55	71	52	77	Recommended
Mikasa 2016 (28)	65	40	35	61	43	33	Recommended with modification
Torres 2017 (29)	74	57	59	67	59	65	Recommended
Qu 2018 (1)	64	33	30	53	21	0	Recommended with modification
Total[a]	61 [51–74]	36 [18–68]	41 [22–59]	56 [47–71]	38 [21–52]	50 [0–77]	

[a], data were presented as mean [range]. AGREE, Appraisal of Guidelines for Research and Evaluation; VAP, ventilator-associated pneumonia.

The distribution of the level of evidence and strength of recommendations of evaluated EBGs is listed in *Table 3*. A total of 558 articles were used as evidence in the 13 EBGs. Seventy-six evidence (13.6%) were classified as level A, 258 (46.2%) as level B, 106 (19.0%) as level C, and 118 (21.2%) as level D. The guideline by Mikasa 2016 (28) had the highest proportion of level A evidence (37.5%), followed by that of Gupta 2012 (25) with 35.6%. Among the 291 recommendations, 148 (50.9%) were rated as strong (grade I), 104 (35.7%) as weak (grade II), and 39 (13.4%) as ungraded (UG). All the recommendations provided by Muscedere 2008a (20) were grade I. Two guidelines (22,24) did not grade the recommendations.

Recommendations for prevention and management

Six guidelines (1,3,20,22,23,25) (46.2%) recommended that empiric (preventive) antibiotic therapy be administered as early as possible, and four (1,25,27,28) (30.8%) recommended that therapy be developed according to local microbiological flora and resistance profiles (*Table 4*). Most guidelines recommend that VAP patients receive an approximately seven-day course of empiric antibiotic therapy. Some guidelines (1,3,25,27,28) recommended a dose de-escalating strategy of antibiotic administration based on different specific situations in order to avoid bacterial resistance. The choice of antibiotics

Table 3 Distribution of the level of evidence and strength of recommendation

Guideline	Level of evidence, No. (%)				Strength of recommendation, No. (%)		
	A	B	C	D	I	II	UG
Dodek 2004 (19)	0 (0)	36 (81.8)	5 (11.4)	3 (6.8)	10 (62.5)	0 (0)	6 (37.5)
Muscedere 2008a (20)	0 (0)	31 (100.0)	0 (0)	0 (0)	8 (100.0)	0 (0)	0 (0)
Muscedere 2008b (21)	4 (6.5)	58 (93.5)	0 (0)	0 (0)	9 (40.9)	4 (18.2)	9 (40.9)
Masterton 2008 (22)	20 (16.8)	25 (21.0)	13 (10.9)	61 (51.3)	–	–	–
Rotstein 2008 (23)	10 (22.2)	21 (46.7)	4 (8.9)	10 (22.2)	15 (33.3)	17 (37.8)	13 (28.9)
Morrow 2009 (24)	3 (18.7)	5 (31.3)	0 (0)	8 (50.0)	–	–	–
Gupta 2012 (25)	16 (35.6)	17 (37.8)	5 (11.1)	7 (15.5)	34 (89.5)	4 (10.5)	0 (0)
Li 2013 (3)	1 (3.2)	15 (48.4)	15 (48.4)	0 (0)	17 (54.8)	14 (45.2)	0 (0)
Klompas 2014 (26)	8 (12.7)	19 (30.1)	34 (54.0)	2 (3.2)	9 (37.5)	15 (62.5)	0 (0)
Kalil 2016 (27)	0 (0)	7 (15.6)	18 (40.0)	20 (44.4)	19 (42.2)	26 (57.8)	0 (0)
Mikasa 2016 (28)	3 (37.5)	5 (62.5)	0 (0)	0 (0)	2 (25.0)	5 (62.5)	1 (12.5)
Torres 2017 (29)	0 (0)	4 (36.4)	6 (54.5)	1 (9.1)	9 (56.3)	6 (37.5)	1 (6.2)
Qu 2018 (1)	11 (28.9)	15 (39.5)	6 (15.8)	6 (15.8)	16 (42.1)	13 (34.2)	9 (23.7)
Total	76 (13.6)	258 (46.2)	106 (19.0)	118 (21.2)	148 (50.9)	104 (35.7)	39 (13.4)

recommended for monotherapy and combination therapy varied among guidelines.

Recommendations for definitive antibiotic therapy in the VAP guidelines are presented in *Table 5*. Six guidelines (46.2%) provided specific recommendations for the treatment of different VAP pathogens. The recommendations of the different guidelines were basically the same for definitive antibiotic therapy. The overall assessment for VAP treatment was that antibiotic treatment regimens be altered according to the pathogen of infection and its susceptibility (1). The timing and schedule of therapy should be adjusted as clinically indicated, which helps reduce unnecessary side effects to improve the clinical outcomes.

There were several recommendations for adjunctive treatments in patients with VAP. One guideline (1) recommended the use of glucocorticoids for patients with severe VAP and hemodynamic instability. Glucocorticoids were not recommended for routine use in three guidelines (1,3,22). Enteral nutrition and immunotherapeutic use were recommended on an individual basis (1). Besides, the use of selective oral decontamination (SOD) was not routinely recommended for the prevention of VAP (*Table 4*). Selective digestive tract decontamination (SDD) (1,3,22,23), nebulized endotracheal antibiotics (3), and oral probiotics (1,3) were also not recommended for routine use. The comparison of recommendations in two recommended guidelines is presented in *Table S2*.

Discussion

EBGs are essential target-based summaries of medical care, whose quality determines the outcomes of clinical application (31). Recently, an increasing number of EBGs pertaining to VAP were developed. Ambaras Khan *et al.* (32) had evaluated the quality of six guidelines, and only two provided specific recommendations for empirical antibiotics and antibiotic de-escalation therapy for VAP. Unfortunately, the EBGs used for VAP were far from complete; in addition, the overall quality of the two EBGs and the levels of evidence used to make them were unclear. Thus, we re-evaluated the 13 identified EBGs pertaining to VAP, and variability in the methodology and quality of these EBGs was found in this study.

Based on the analysis of the AGREE II quality score, the highest-scoring domain was found with the *scope and purpose* followed by c*larity of presentation* domains (*Table 2*), which indicated that most guidelines fully satisfied these criteria.

Table 4 Comparison of recommendations for empiric antibiotic therapy and medicine prevention of VAP[a]

Category	Recommendations	Source
Time to initiate therapy	Start immediately when the patient was clinically suspected with	Muscedere 2008a (20) (A); Masterton 2008 (22) (B); Gupta 2012 (25) (1A)
	Start within 24 hours of diagnosing VAP	Rotstein 2008 (23) (2B); Li 2013 (3) (1C)
	Start as early as possible after diagnosing VAP	Qu 2018 (1) (3A)
Duration of treatment	7 d	Gupta 2012 (25)[b] (1A); Kalil 2016 (27)[b] (1B)
	7–8 d	Rotstein 2008 (23)[b] (1A); Torres 2017 (29) (2B)
	7–10 d	Li 2013 (3)[b] (1B)
	≥7 d	Qu 2018 (1)[b]
	≤8 d	Muscedere 2008a (20); Masterton 2008 (22) (B)
Monotherapy *vs.* combination therapy	Monotherapy	Muscedere 2008a (20); Masterton 2008 (22) (A)
	Combination therapy	Gupta 2012 (25) (D)
	Monotherapy therapy for general situation; combination therapy when came to MDROs	Li 2013 (3) (1B); Mikasa 2016 (28) (1A); Qu 2018 (1) (1C)
Medicine prevention	Recommend SOD	Muscedere 2008b (21); Rotstein 2008 (23); Mikasa 2016 (28) (1A)
	Not recommend SOD	Morrow 2009 (24)[c] (B); Klompas 2014 (26)[c] (1B); Torres 2017 (29) (UG); Qu 2018 (1) (1B)
	Not recommend SDD	Masterton 2008 (22)[d] (C); Rotstein 2008 (23) (2D); Qu 2018 (1) (1B)
	Not recommend inhaled antibiotic	Li 2013 (3) (2C)
	Not recommend oral probiotics	Li 2013 (3) (2B); Qu 2018 (1) (2B)
	Nutritional support via nasal intestine	Li 2013 (3) (2B)

[a], some level of evidences and strength of recommendation were not listed in the table since the original literature didn't provide; [b], when it came to poor clinical efficacy, infection of MDROs or immune function defects, extension of antibiotic therapy course was recommended appropriately; [c], recommendation only for pediatric patients; [d], when mechanical ventilation will be for ≥48 h, SDD should be considered for ICU patients. VAP, ventilator-associated pneumonia; MDROs, multidrug-resistant organisms; SOD, selective oral decontamination; SDD, selective digestive tract decontamination.

Most guidelines could fully describe the overall objective, target population and their specific clinical issues (33). Guidelines with well adherence to these key information appeared to be more easily accepted and accessed by its intended users (34). What's more, adhering to the aspects of these domains does not require a great deal of human power, financial and material resources.

The potential for improvements is needed in several domains. *Stakeholder involvement* had the lowest score among AGREE II domains. Implementation of guidelines requires contribution and expertise of multidisciplinary medical team (including clinical experts, methodological experts, health economists, etc.), coupled with the target population' values and preference of healthcare, so as to ensure that recommendations are advisable, unbiased, and reliable (35,36). However, only two (15.4%) guidelines provided details regarding involvement of patients or the public, and seven (53.8%) included these experts in the guidelines we reviewed. Owing to limited information regarding relevant tools for their application and possible barriers, *applicability* scored disturbingly low. This indicated that guideline developers may not understand the value and importance of the components of the domain and items (including the implementation of pilot testing, economic assessment, educational tools and patient leaflets, etc.). Most notably, the guidelines lacking clinical applicability were a

Table 5 Comparison of recommendations for definitive antibiotic therapy of VAP[a]

Guideline	MRSA	Ab	P. Aeruginosa	ESBLs-producing Enterobacteriaceae
Masterton 2008 (22)	No firm conclusion can be reached on the use of linezolid or a glycopeptide (UG)	Not applicable	Ceftazidime, ciprofloxacin, meropenem, piperacillin/tazobactam (UG)	Not applicable
Gupta 2012 (25)	Vancomycin (1A), teicoplanin (1B); linezolid[b] (1A)	MDR: carbapenems (1A), COlistin (1A), polymyxin B (1B), sulbactam & colistin (2B), sulbactam & carbapenem (2B)	MDR: a carbapenem & (a fluoroquinolone or an aminoglycoside) (1A)	Not applicable
Li 2013 (3)	Glycopeptides (vancomycin), linezolid, tetracycline[b]	Sulbactam and its mixture (ceftazidime/sulbactam), carbapenem (imipenem); combined with aminoglycoside, tetracycline, quinolone, polymyxin E	Cephalosporins (ceftazidime), carbapenems (imipenem), beta-lactamase inhibitors (ceftazidime & sulbactam); combined with quinolones or aminoglycosides	Beta-lactamase inhibitors (ceftazidime/sulbactam), carbapenems (imipenem), tetracyclines
Kalil 2016 (27)	Vancomycin, linezolid[b] (1B)	Carbapenem, ampicillin/sulbactam (2C); polymyxin (colistin or polymyxin B) (1C)	Against aminoglycoside monotherapy (1D)	Based upon the results of antimicrobial susceptibility testing and patient-specific factors (1D)
Mikasa 2016 (28)	Glycopeptides (vancomycin, teicoplanin) or linezolid (1A)	Not applicable	As oral drugs: new quinolones; as injection: anti-P. aeruginosa penicillins, cephems, monobactums, carbapenems, or new quinolones	Imipenem, ceftazidime/sulbactam, meropenem, doripenem
Qu 2018 (1)	Glycopeptides (vancomycin, teicoplanin), linezolid	Sulbactam and its mixture, carbapenems (imipenem), polymyxins, tigecycline, aminoglycosides (amikacin), quinolones; MDR: sulbactam and its mixture (dose: 6–8 g/d), carbapenems[c]; XDR or PDR: polymyxin & (sulbactam and its mixture, carbapenems, aminoglycosides, tigecycline)	Cephalosporins (ceftazidime), carbapenems (imipenem), beta-lactamase inhibitors (ceftazidime/sulbactam), quinolones, aminoglycosides, polymyxin; MRD: beta-lactams & (aminoglycosides or quinolones or fosfomycin); XDR: polymyxin & beta-lactam & (ciprofloxacin or fosfomycin)	Mild to moderate infection: cephalosporin (cefoxitin), oxygen cephem, beta-lactamase inhibitor (ceftazidime/sulbactam); moderate to severe infection: carbapenems, carbapenems & (quinolones or aminoglycosides), beta-lactamase inhibitor cocktails & (quinolones or aminoglycosides)

[a], level of evidence and strength of recommendation are not listed in the table when the original literature did not provide it; [b], it were recommended as an alternative to vancomycin in patients with vancomycin intolerance, renal failure, and vancomycin-resistant organisms; [c], the dose of this antibiotics given or extending treatment time should be increased for the infection of MDR. MRSA, methicillin-resistant staphylococcus aureus; Ab, acinetobacter baumannii; P. Aeruginosa, pseudomonas aeruginosa; ESBLs-producing enterobacteriaceae, extended-spectrum beta-lactamases producing enterobacteriaceae; MDR, multiple drug resistance; XDR, extensive drug resistance; PDR, pan drug resistance; VAP, ventilator-associated pneumonia.

complete waste of money and time. *Rigor of development* was considered the most crucial domain in the assessment of guideline development. This domain evaluated the methods used in guideline development, including the methods used to search the literature, identify evidence, evaluate the quality of the evidence, and how recommendations were derived (35-37). Reporting all methodological aspects is therefore particularly essential to allow the intended guideline users to judge the validity of the content. Nevertheless, none of the guidelines scored above 60% in this domain, and only seven (53.8%) guidelines reported the methods used to perform the systematic literature search.

The grading system used for evaluating the level of evidence and strength of recommendation varied among different guidelines, which might lead to confusion among the guideline users as to how they are used in clinical practice (38,39). There is a need for a standardized grading system. Although the majority of recommendations were classified as grade I, many were derived from low- or poor-quality evidence. This could be due to an inadequate literature search strategy that did not identify high-quality evidence or that such evidence does not indeed exist. Improved methods to search the literature and identify best evidence supporting the recommendation will have the largest impact on this point. Besides, an increasing number of clinical research centers, which allows for greater coordination of studies and increases the investment in research funding, greatly contributes to the development of more high-quality evidence.

An important level of consensus appears for the recommendations throughout the various EBGs. However, there are some conflicts mainly in the drug choice and adjustment of empirical and targeted antibiotic therapies, which plays an important role in the management of VAP (1). There are four main reasons contributing to the variances: (I) developers are inclined to develop guidelines based on local conditions and indigenized evidence, such as differences in the variance of pathogens and its drug resistance; (II) owing to the different publication time of EBGs, the timely updated evidence could lead to the changes of recommendations; (III) recommendations may be constructed on the opinions of personal experts but not the trustworthy consensus statements because of the scant or imperfect evidence; (IV) the expectation and preference of the public or patients may influence the ultimate recommendations in EBGs. Thus, a local and updated guideline could provide more useful and reliable information for clinicians.

We made the following recommendations to improve the quality of guidelines. First, the methodological quality should be stringently scrutinized and censored, and randomized trials should be conducted before widespread implementation of guidelines. Second, guidelines should also be periodically reassessed and updated in a timely manner to improve the quality of guidelines. Third, more high-quality further studies are needed to strengthen the evidence and resolve controversy of guidelines. Fourth, consensus on a standardized grading system for the quality of evidence and strength of recommendations must be reached. Furthermore, strengthen the international collaboration to make regulations to develop a guideline framework on guideline development and improve the quality of the guidelines.

Limitations and strengths

Our study has several strengths. A comprehensive and systematic search of the literature was performed and agreement regarding the findings was achieved between two review teams. The AGREE II instrument was used to test guideline assessment and the methodological quality of EBGs.

Limitations included a literature search of only English and Chinese publications. The AGREE II instrument focuses on assessing the methods of guideline development and transparency of reporting. It does not assess the potential impact of recommendations on patient outcomes. The minimal reporting of how the guidelines were derived varied may have contributed to lower assessment scores.

Conclusions

The overall quality of VAP EBGs was moderate. Significant shortcomings, particularly in the *stakeholder involvement*, *rigor of development* and *applicability* domains, were observed. The grading system used to evaluate levels of evidence and strength of recommendation should be unified in future guidelines. The category, methods of use, and course of antibiotics administered to prevent or manage VAP varied by guideline. More high-quality evidence is needed to improve guideline recommendations.

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Footnote

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Supplementary

Table S1 A composite grading system for ranking evidence and recommendation

Grade	Notes	Symbol
Quality of evidence		
High	Randomized controlled trials without important limitations or meta-analysis or double-upgraded observational studies. Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Downgraded randomized controlled trials; upgraded observational studies. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Double-downgraded randomized controlled trials; observational studies; case series/case reports. Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate	C
Very low	Triple-downgraded randomized controlled trials; downgraded observational studies; expert opinion. Further research is most likely to have an important impact on our confidence in the estimate of effect and change the estimate probably. Any estimate of effect is uncertain	D
Strength of recommendation		
Strong recommendation	Good evidence to support a recommendation for use or against use. Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost	I
Weaker recommendation	Moderate evidence to support a recommendation for use or against use. Variability in preferences and values or greater uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	II
Ungraded recommendation	Poor evidence to support a recommendation. The pros and cons of taking interventions are quite unclear. Failed to identify target population	UG

Table S2 The comparison of recommendations in recommended VAP guidelines

Variable	International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia (Torres 2017) (29)	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 (Kalil 2016) (27)
General characteristics		
Patient population	Adults	Adults
Institution/ development group	ERS; ESICM; ESCMID and ALAT	IDSA and ATS
Focus of guideline	Treatment/prevention	Treatment
Origin	Europe, Latin America	America
Journal of publication	European Respiratory Journal	Clinical Infectious Diseases
Number of references	133	364
Number of questions	7	25
AGREE II scores		
Scope and purpose	74	71
Stakeholder involvement	57	68
Rigor of development	59	55
Clarity and presentation	67	71
Applicability	59	52
Editorial independence	65	77
Overall score	62	63
Level of evidence, No. (%)		
A	0 (0)	0 (0)
B	4 (36.4)	7 (15.6)
C	6 (54.5)	18 (40.0)
D	1 (9.1)	20 (44.4)
Strength of recommendation, No. (%)		
I	9 (56.2)	19 (42.2)
II	6 (37.5)	26 (57.8)
UG	1 (6.3)	0 (0)
Recommendations on several problems		
Definitions of VAP	VAP is one specific type of HAP	Patients with HAP or VAP belong to two distinct groups
Microbiologic sampling diagnosis	It suggested to obtain adequate sputum samples in stable patients with suspected VAP (2C)	It is suggested to obtain adequate sputum samples in patients with suspected VAP (2C)
Empiric therapy	It suggested to use narrow-spectrum antibiotics (ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin) in patients with suspected low risk of resistance and early-onset VAP (2D)	It suggested to administer antibiotics effective against S. aureus, Pseudomonas aeruginosa, and other gram-negative bacilli in all empiric regimens in patients with suspected VAP (1C)
De-escalated antibiotic therapy	It suggested that the initial empiric or therapeutic combination antibiotic for high-risk VAP patients be de-escalated rather than fixed for patients without XDR/ PDR non-fermenting gram-negative bacteria and CRE isolates	It suggested that antibiotic therapy be de-escalated rather than fixed (2D)
Duration treatment	A 7–8-day course of antibiotic therapy in patients with VAP is usually recommended (2B)	A 7-day course of antimicrobial therapy is recommended (1D)
Prevention	No recommendation was made for the use of chlorhexidine for SOD in patients requiring mechanical ventilation due to the lack of safety data (UG)	Not applicable

VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; XDR, extensive drug resistance; PDR, pan drug resistance; CRE, carbapenem-resistant enterobacteriaceae.