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INVITED ARTICLE QUALITY IMPROVEMENT

Trish M. Perl, Section Editor

Quality Indicators to Measure Appropriate Antibiotic Use in Hospitalized Adults

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Background. An important requirement for an effective antibiotic stewardship program is the ability to measure appropriateness of antibiotic use. The aim of this study was to develop quality indicators (QIs) that can be used to measure appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized adult patients.

Methods. A RAND-modified Delphi procedure was used to develop a set of QIs. Potential QIs were retrieved from the literature. In 2 questionnaire mailings with an in-between face-to-face consensus meeting, an international multidisciplinary expert panel of 17 experts appraised and prioritized these potential QIs.

Results. The literature search resulted in a list of 24 potential QIs. Nine QIs describing recommended care at patient level were selected: (1) take 2 blood cultures, (2) take cultures from suspected sites of infection, (3) prescribe empirical antibiotic therapy according to local guideline, (4) change empirical to pathogen-directed therapy, (5) adapt antibiotic dosage to renal function, (6) switch from intravenous to oral, (7) document antibiotic plan, (8) perform therapeutic drug monitoring, and (9) discontinue antibiotic therapy if infection is not confirmed. Two QIs describing recommended care at the hospital level were also selected: (1) a local antibiotic guideline should be present, and (2) these local guidelines should correspond to the national antibiotic guidelines.

Conclusions. The selected QIs can be used in antibiotic stewardship programs to determine for which aspects of antibiotic use there is room for improvement. At this moment we are testing the clinimetric properties of these QIs in 1800 hospitalized patients, in 22 Dutch hospitals.

Keywords. quality indicator; quality improvement; antibiotic treatment; appropriate antibiotic use; antibiotic stewardship.

The World Health Organization signaled the emergence of antibiotic resistance, along with the steady decline in the discovery of new antibiotics, as a major health threat for the coming decade. To help control antibiotic resistance, better use of current agents is warranted and a decrease in inappropriate use of antibiotics is necessary [1].

Antibiotic stewardship is an active interprofessional effort by multidisciplinary teams to optimize clinical outcome while minimizing unintended consequences of antibiotic use, including the emergence of resistance [2]. Literature shows that stewardship programs can decrease incorrect antibiotic use and reduce healthcare costs without negatively influencing the quality of care provided [2]. An important requirement for an effective stewardship program to set priorities and focus improvement is the ability to measure the appropriateness of hospital antibiotic use.

Guidelines on the management of infections describe, by definition, appropriate antibiotic use [3]. Adherence to such guidelines improves clinical outcome, is correlated with a lower rate of development of resistance to antibiotics, and lowers costs [4–8]. Available guidelines and international literature can be used to systematically develop precise parameters, so-called quality indicators (QIs), to measure the appropriateness of antibiotic use [9–11]. The European Surveillance of Antimicrobial Consumption developed QIs to measure appropriate outpatient antibiotic use in Europe [12]. However, at

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this moment generic antibiotic use indicators—that is, indicators for measuring the appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized patients—are not available, but they are increasingly requested by policy makers.

The aim of this study was to develop a set of generic indicators that can be used to assess the appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized adult patients.

METHODS

We applied the RAND modified Delphi method to develop a set of QIs for appropriate antibiotic use in the treatment of all bacterial infections in hospitalized adult patients, with the exception of patients treated in the intensive care unit (ICU) (Figure 1) [13, 14].

Literature Search

To create an inventory of already available QIs, we searched the databases of PubMed and Embase to identify studies regarding the development or evaluation of QIs for antibiotic use in hospitalized adults. The search strategies are listed in Figure 2*A* and 2*B*.

First, the abstracts were screened. Included were articles describing QIs for bacterial infections or antibiotic prescribing in hospitalized adult patients, excluding ICU

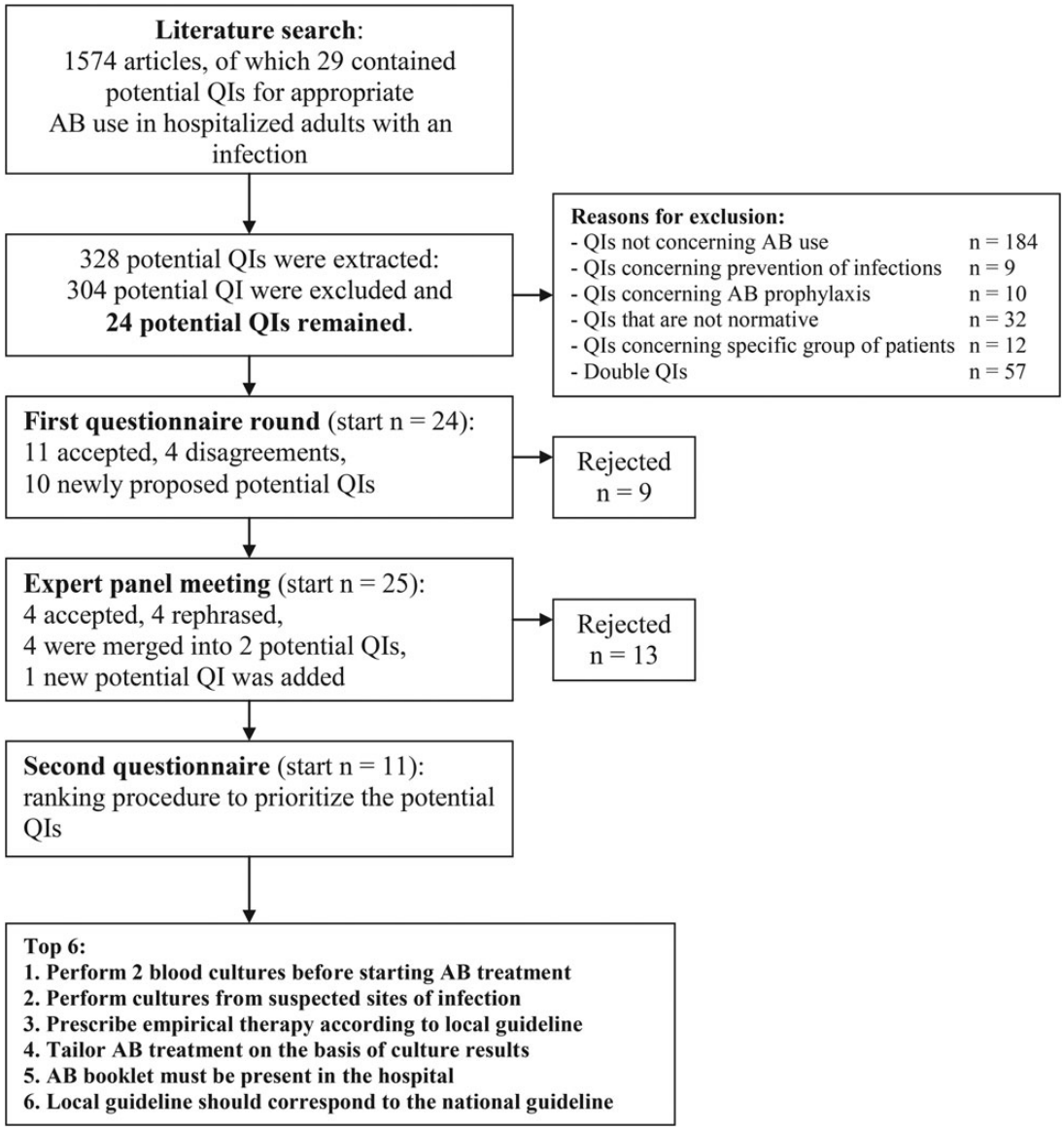

Figure 1. The RAND-modified Delphi procedure. Abbreviations: AB, antibiotic; QI, quality indicator.

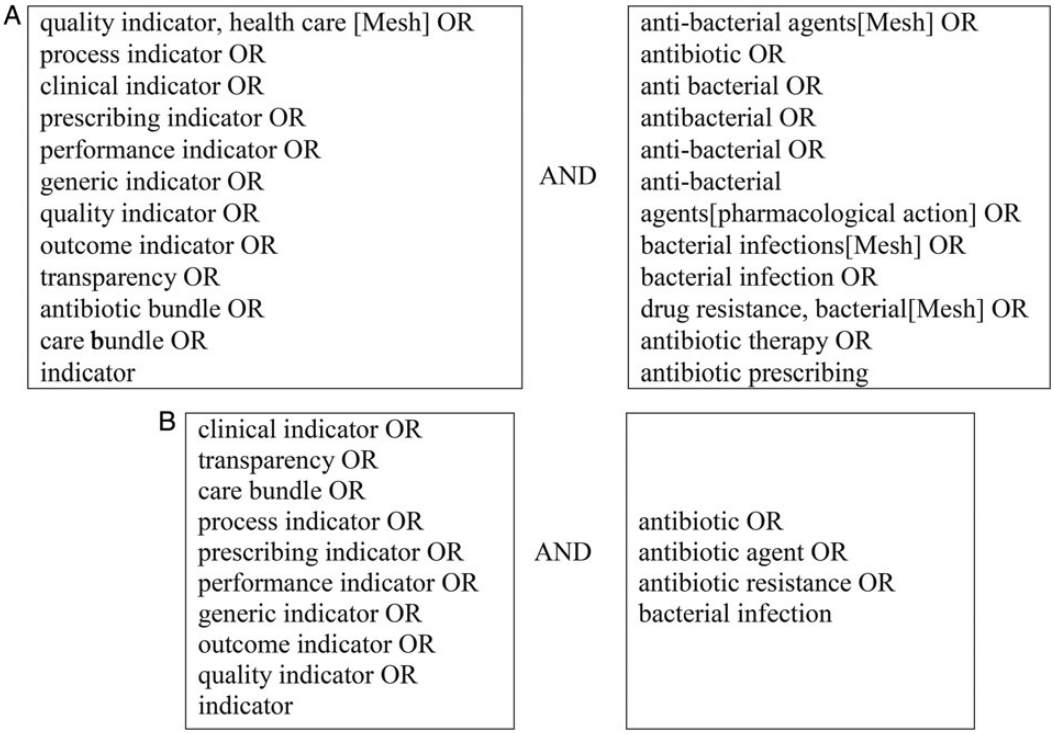

Figure 2. *A*, Search strategy in Medline. Limits: humans, English, French, German, Italian, Spanish, Dutch. *B*, Search strategy in Embase. Limits: not animals, English, French, German, Italian, Spanish, Dutch, not case reports.

patients. Potentially relevant publications were checked in full-text format.

Next, from these included publications, potentially relevant indicators regarding antibiotic prescribing/use were extracted, after which the exclusion criteria were applied (Figure 1). QIs were excluded if they did not concern antibiotic use, were specified for a specific group of patients, concerned antibiotic prophylaxis, or were not normative. This process of excluding QIs was done by 3 reviewers (C. v. d. B., S. E. G., and J. M. P.), who also determined the level of supporting evidence (Tables 1 and 2).

Table 1. Methodological Quality of Individual Studies

	Intervention	Etiology, Prognosis
A1	Systematic review of at least 2 independent A2-level studies	
A2	Randomized controlled trial of sufficient methodological quality and power	Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative study lacking the same quality as mentioned at A2 (including patient-control and cohort studies)	Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study, or patient-control study
C	Noncomparative study	
D	Expert opinion	

First Questionnaire Round

The list of the potentially relevant QIs was converted into a written questionnaire and used for the RAND-modified Delphi method to achieve expert consensus on these QIs.

We invited 20 experts from different countries and different specialties. All but 3 of the invited experts consented to participate in this survey. Ultimately, our international expert panel was composed of 17 members from the Netherlands, Spain, Belgium, Scotland, Croatia, and Sweden, and consisted of 5 medical microbiologists, 4 infectious disease specialists, 2 clinical hospital pharmacists, 2 general surgeons, 2 pulmonologists, and 2 gynecologists (Supplementary Appendix 1).

We asked the experts (panel members) to appraise the potential QIs while considering the following criteria:

- The recommended care leads to health gain for the patient or to less bacterial resistance, or promotes efficiency of care;

Table 2. Level of Evidence of Conclusions

	Conclusions Based on Following Level
1	Study of level A1 or at least 2 independent studies of level A2
2	One study of level A2 or at least 2 independent studies of level B
3	One study of level B or C
4	Expert opinion

- The recommended care is generalizable to all adult patients treated with antibiotics for a bacterial infection;
- There is sufficient scientific evidence or expert consensus to justify the recommended care.

To rate the degree with which the potential QI described appropriate antibiotic use (in accordance with these criteria), a Likert scale was used ranging from 1 ("definitely not appropriate care") to 9 ("definitely appropriate care"), including an answer category "cannot assess." The panel members could rephrase the potential indicator and could add new items and/or QIs.

The results from the first questionnaire were analyzed using a standardized Microsoft Access–based consensus tool. QIs with a median score of 8 or 9 were accepted if there was no disagreement. Disagreement was defined as the case in which <70% of the scores were in the top tertile (scores 7, 8, or 9). If there was disagreement and the median score was ≤7, the QI was rejected. The QIs with a median score of 8 or 9 with disagreement or a median score of 7 without disagreement were discussed during the consensus meeting [15].

Expert Panel Meeting

For pragmatic reasons, only Dutch panel members (n = 12) were invited for the expert panel meeting. The goal of the meeting was to present the results after the first round and to discuss the QIs with a median score of 8 or 9 with disagreement or a median score of 7 without disagreement. In addition, newly added potential QIs were discussed, and accepted QIs with comments from the experts were rephrased in consensus.

Second Questionnaire Round, Ranking Procedure

After the consensus meeting, all of the accepted, added, and rephrased potential QIs were presented again in a questionnaire for final remarks, approval of the panel members, and prioritization of the potential QIs by asking the panel members to select a personal "top 5" of most relevant QIs. An extensive summary with the results from the consensus meeting was sent to the panel members together with the second questionnaire.

Rephrased indicators were accepted if at least 70% of the experts agreed with the new formulation. When an indicator was mentioned first in a panelist's "top 5," it was granted 5 points; the second was given 4 points, the third indicator was granted 3 points, and so on. QIs receiving >15% of the maximum possible ranking points were considered to be the most important QIs for antibiotic care in all adult patients with a bacterial infection.

RESULTS

Literature Search

Of the 1574 identified articles regarding bacterial infections and/or antibiotic prescribing, 46 provided QIs, of which 29 articles described QIs for hospitalized adult patients, with the exception of patients treated in the ICU. From these 29 articles we derived 328 QIs, which also included 5 systematically developed, but at that moment not yet published QIs regarding antibiotic treatment in hospitalized adults with sepsis [16] (see Supplementary Appendix 2 for these 29 articles). With 3 reviewers, we applied the predefined exclusion criteria and 304 QIs were excluded, mostly because they did not concern antibiotic use (184 QIs) or were doubles (57 QIs) (Figure 1). This resulted in 24 potential generic QIs. These 24 potential QIs were put into a written questionnaire and sent to the 17 panel members (Table 3, numbers 1–24).

First Questionnaire Round

The consensus procedure was performed between May and October 2011. Sixteen members of the panel (all except 1 general surgeon) returned the first questionnaire (94% response). Eleven of the 24 initial indicators were accepted and 9 indicators were rejected (Figure 1 and Table 3). The panel members disagreed on 4 potential QIs, and 10 new potential QIs were suggested (Table 3, numbers 29, 33–41).

Expert Panel Meeting

Five (29%) Dutch panel members (1 medical microbiologist, 2 infectious disease specialists, 1 clinical hospital pharmacist, and 1 general surgeon) attended the consensus meeting. Discussed were the 11 accepted QIs with comments, the 4 with disagreement or a median score of 7, and the 10 newly proposed indicators from the first questionnaire round. Comments from the panel members regarding the first questionnaire were used to rephrase some of the accepted indicators. All 4 potential QIs requiring discussion and 9 of the 10 newly proposed QIs were rejected. From the 11 previously accepted indicators, 4 indicators were rephrased, 3 remained unchanged, and another 4 indicators were merged into 2 indicators with similar content (Table 3). One additional potential QI was added during the meeting.

Second Questionnaire Round, Ranking Procedure

During the second questionnaire round, 11 potential QIs were presented to all panel members for final remarks and approval. All 17 questionnaires were returned (100% response) and no indicator was excluded, as ≥70% of the panelists agreed with each new formulation. The ranking of this entire set of indicators resulted in 6 QIs with the highest scores (Table 3).

Final Set of Selected QIs

Table 4 shows the entire set of 11 QIs representing the final, valid set of QIs that can be used to measure the appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized adult patients.

Table 3. Results of the Delphi Procedure: First Questionnaire, Consensus Meeting, and Second Questionnaire

		First Questionnaire				Second Questionnaire		
Quality Indicators	Level of Supporting Evidence (See Tables 1 and 2)	Median	% in Highest Tertile	Conclusion	Consensus Meeting	No. of Experts	Total Score	Conclusion
1. In hospitalized adults with a suspected bacterial infection, empirical therapy should be started intravenously.	4	6	47	Rejected[a]				
2. In hospitalized adults with a suspected bacterial infection, empirical therapy should be started as soon as possible, preferably within the first hour of presentation.	2	8	57	Discuss[b]	Rejected			
3. In hospitalized adults with a suspected bacterial infection, empirical therapy should be started within 4 h after clinical presentation.	2 (pneumonia) 4 (UTIs)	7	69	Rejected				
4. In hospitalized adults with a suspected bacterial infection, empirical therapy should be started within 8 h after arrival in the emergency department.	2	7	53	Rejected				
5. In hospitalized adults with a suspected bacterial infection, empirical therapy should be administered while the patient is in the emergency department.	2	6	50	Rejected				
6. Before starting systemic antibiotic therapy in hospitalized adults with a suspected bacterial infection, at least 2 sets of blood cultures should be taken.	2 (severe pneumonia) 3 (sepsis)	8	80	Accepted[c]	Accepted	7	15	Accepted and selected for top 6
7. Blood cultures before start of antibiotics should be obtained from hospitalized patients with a suspected bacterial infection and the clinical indication listed here: ICU admission, cavitary infiltrates, leukopenia, active alcohol abuse, chronic severe liver disease, asplenia, or pleural effusion.	2	8	53	Discuss	Rejected			
8. Before starting antibiotic therapy in hospitalized adults with a suspected bacterial infection, specimens for culture from suspected sites of infection should be taken.	4	8	94	Accepted	Rephrased into number 26			
9. Before starting antibiotic therapy in hospitalized adults with a suspected bacterial infection, Gram stain of a specimen from the suspected site of infection should be performed.	4	5	27	Rejected				
10. In hospitalized adults with a suspected bacterial infection, empirical therapy should be prescribed according to the national guideline.	2 (intra-abdominal infections) 3 (pneumonia)	8	93	Accepted	Merged[d] into indicator number 25			
11. The choice of initial antibiotics should be empirical, but should clearly be guided by the clinical picture and the sensitivity patterns of local pathogens.	2	8	73	Accepted	Merged into indicator number 25			
12. When prescribing empirical therapy in hospitalized adults with a suspected bacterial infection, local guidelines should correspond to the national guideline and can only deviate on legitimate grounds.	4	8	81	Accepted	Rephrased into indicator number 32			

Table 3 continued.

Quality Indicators	Level of Supporting Evidence (See Tables 1 and 2)	First Questionnaire			Consensus Meeting	Second Questionnaire		
		Median	% in Highest Tertile	Conclusion		No. of Experts	Total Score	Conclusion
13. In hospitalized adults with a suspected bacterial infection, empirical treatment with fluoroquinolones should only be used if oral therapy is given or in case of anaphylaxis related to β-lactam antibiotics.	3	6	33	Rejected				
14. In hospitalized adults with a suspected bacterial infection, dose and dosing interval of antibiotics should be adapted to renal function.	4	8	88	Accepted	Accepted	2	3	Accepted
15. In hospitalized adults with a suspected bacterial infection, empirical antibiotics should be changed to pathogen-directed therapy if culture results become available.	3 (all infections) 4 (UTIs and pneumonia)	9	88	Accepted	Accepted	11	23	Accepted and selected for top 6
16. In hospitalized adults with a bacterial infection, antibiotic therapy should be switched from IV to oral antibiotic therapy after 48–72 h on the basis of the clinical condition.	1 (pneumonia) 2 (all infections) 3 (UTIs)	8	80	Accepted	Rephrased into indicator number 27			
17. Hospitalized adults with a bacterial infection should be switched from intravenous to oral antibiotics within 24 h of being candidates for switch therapy. Criteria for switching: (1) clinical symptoms are improving, (2) patient is afebrile for at least 8 h, (3) the white blood cell count is normalizing, (4) oral intake and gastrointestinal absorption are adequate.	2	7	56	Rejected				
18. Hospitalized adults with a bacterial infection should be switched from intravenous to oral antibiotics when the patient meets all of the following criteria: a clinically improving condition, hemodynamic stability, and tolerance of oral medication or food and fluids.	2	8	67	Discuss	Rejected			
19. When antibiotic therapy was started in a hospitalized adult, the actual length of treatment should be in accordance with the length mentioned in the patient's medical file.	4	5	15	Rejected				
20. If the presenting clinical syndrome in a hospitalized adult is determined to be due to a noninfectious cause, antibiotic therapy should be stopped promptly.	2	9	88	Accepted	Rephrased into indicator number 30			
21. In a hospitalized adult with a suspected bacterial infection who was initially started on IV antibiotic therapy, the possibility of IV-oral switch should be documented in case notes.	4	6	50	Rejected				
22. In a hospitalized adult with a suspected bacterial infection, the indication to start antibiotics should be documented in case notes.	4	8	86	Accepted	Merged into indicator number 28			

Table 3 continued.

Quality Indicators	Level of Supporting Evidence (See Tables 1 and 2)	First Questionnaire			Consensus Meeting	Second Questionnaire		
		Median	% in Highest Tertile	Conclusion		No. of Experts	Total Score	Conclusion
23. In a hospitalized adult with a suspected bacterial infection who was started on antibiotic therapy, an antibiotic plan (name, dose, route, interval of administration, and planned duration) should be documented in case notes.	4	8	79	Accepted	Merged into indicator number 28			
24. In a hospitalized adult with a suspected bacterial infection who was started on antibiotic therapy, a review of the diagnosis should be documented in case notes.	4	7	77	Discuss	Rejected			
25. In hospitalized adults with a suspected bacterial infection, empirical systemic antibiotic treatment should be prescribed according to the local guideline. (If local guidelines are missing, prescribe according to national guideline. If national guidelines are also missing, prescribe according to international guidelines.)					Result from merging indicators numbers 10 and 11	13	25	Accepted and selected for top 6
26. When starting systemic antibiotic therapy in hospitalized adults with a suspected bacterial infection, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started. (Cultures should be taken until maximal 24 h after antibiotics are started.)					Result from rephrasing indicator number 8	6	13	Accepted and selected for top 6
27. In hospitalized adults with a bacterial infection, systemic antibiotic therapy should be switched from IV to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate. Adequate: (1) when antibiotic is available orally, (2) when oral intake and gastrointestinal absorption are adequate, (3) adequate in terms of diagnosis (exceptions like endocarditis, meningitis).					Result from rephrasing indicator number16	3	4	Accepted
28. In a hospitalized adult with systemic antibiotic therapy, an antibiotic plan should be documented in the case notes at the start of treatment (indication, name, doses, route, interval of administration).					Result from merging indicator numbers 22 and 23	2	5	Accepted
29. Therapeutic drug monitoring should be performed when the treatment duration is >3 d for aminoglycosides and >5 d for vancomycin.				Added[e]	Accepted as new indicator	1	1	Accepted
30. Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be 7 d.					Result from rephrasing indicator number 20	3	7	Accepted

Table 3 continued.

Quality Indicators	Level of Supporting Evidence (See Tables 1 and 2)	First Questionnaire			Consensus Meeting	Second Questionnaire		
		Median	% in Highest Tertile	Conclusion		No. of Experts	Total Score	Conclusion
Process indicators:								
31. A current local antibiotic guideline should be present in the hospital and an evaluation on whether an update should be considered should be done:					Added[e]			Accepted and selected for top 6
- every year?						2		
- every 2 years?						7		
- every 3 years?						7		
- every 5 years?						1		
32. Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.					Result from rephrasing indicator number 12			Accepted and selected for top 6
33. When not to treat (asymptomatic UTI, MRSA in sputum, contamination, etc)				Suggested new topic/QI	Rejected			
34. Dose of antibiotic therapy				Suggested new topic/QI	Rejected			
35. Prescribing according to PK/PD principles				Suggested new topic/QI	Rejected			
36. Appropriate microbiological specimens also for viruses				Suggested new topic/QI	Rejected			
37. Rapid urine antigen test in severe pneumonia				Suggested new topic/QI	Rejected			
38. Documenting clinical outcomes and treatment failures				Suggested new topic/QI	Rejected			
39. Documenting severity of sepsis in case notes at start of treatment				Suggested new topic/QI	Rejected			
40. Broad-spectrum IV therapy for patients with severe sepsis				Suggested new topic/QI	Rejected			
41. Length of antibiotic treatment				Suggested new topic/QI	Rejected			

Abbreviations: ICU, intensive care unit; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PD, pharmacodynamic; PK, pharmacokinetic; QI, quality indicator; UTI, urinary tract infection.

[a] Rejected: disagreement between panel members and the median was also <8; the potential indicator was deselected and not discussed during the consensus meeting.

[b] Discussion: the QI had a median score of 7 without disagreement or a median score of 8 or 9 with disagreement, and so it was discussed during the consensus meeting.

[c] Accepted: the potential QI was selected for the next round because of an overall median score of 8 or 9, without disagreement. Disagreement was defined as the case in which <70% of the scores were in the top tertile (score of 7, 8, or 9).

[d] Merged: multiple indicators were "rejected" and merged into a composite, more generic indicator.

[e] Added: the indicator was proposed by one of the experts and was added to the initial set of indicators. Supporting evidence varied sometimes between populations (adults with pneumonia or with sepsis or with complicated UTI).

Table 4. Final List of Quality Indicators to Monitor Antibiotic Use for All Bacterial Infections in Hospitalized Adult Patients in Non–Intensive Care Unit Departments

Number From Table 1	Quality Indicator All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection	Numerator Description All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection	Denominator Description All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection
25	Empirical systemic antibiotic therapy should be prescribed according to the local guideline. (If local guidelines are missing, prescribe according to national guideline. If national guidelines are also missing, prescribe according to international guideline.)	Number of patients who started with empirical systemic antibiotic therapy according to the local guideline	Total number of patients who started with empirical systemic antibiotic therapy
6	Before starting systemic antibiotic therapy, at least 2 sets of blood cultures should be taken.	Number of patients in whom at least 2 blood cultures were taken before systemic antibiotic therapy was started	Total number of patients who started with systemic antibiotic therapy
26	When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started. (Cultures should be taken until a maximum of 24 h after antibiotics are started.)	Number of patients who started with systemic antibiotic therapy and in whom cultures from suspected sites of infection were taken within 24 h after the systemic antibiotics were started	Total number of patients who started with systemic antibiotic therapy
15	Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available	Number of patients with empirical systemic antibiotics whose culture became positive and changing to pathogen-directed therapy was done correctly	Total number of patients with empirical systemic antibiotics whose culture became positive
14	Dose and dosing interval of systemic antibiotics should be adapted to renal function.	Number of patients with a compromised renal function with a dosing regimen adjusted to renal function (defined as eGFR <50 mL/min/1.73 m^2)	Total number of patients who started with systemic antibiotic therapy and who had a compromised renal function (defined as eGFR <50 mL/min/1.73 m^2)
27	Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate. Adequate: (1) when antibiotic is available orally, (2) when oral intake and gastrointestinal absorption are adequate, (3) adequate in terms of diagnosis (exceptions, eg, endocarditis, meningitis)	Number of patients with intravenous antibiotics for 48–72 h, in whom changing to oral antibiotic therapy on the basis of clinical condition was done	Total number of patients with intravenous antibiotics for 48–72 h, in whom changing to oral antibiotic therapy on the basis of the clinical condition was indicated
28	An antibiotic plan should be documented in the case notes at the start of systemic antibiotic treatment (Antibiotic plan is indication, name, doses, route, and interval of administration.)	Number of patients who started with systemic antibiotic therapy for whom an antibiotic plan was documented in the case notes	Total number of patients who started with systemic antibiotic therapy
29	Therapeutic drug monitoring should be performed when the treatment duration is >3 d for aminoglycosides and >5 d for vancomycin.	Number of these patients with at least 1 serum drug level measurement	Total number of patients who received aminoglycosides for >3 d and/or vancomycin for >5 d
30	Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be 7 d.	Number of patients whose empirical antibiotic therapy was discontinued within 7 d, because of lack of clinical and/or microbiological evidence of infection	Total number of patients who started empirical systemic antibiotic therapy, but lacked clinical and/or microbiological evidence of infection

Table 4 continued.

Number From Table 1	Quality Indicator All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection	Numerator Description All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection	Denominator Description All Patients Are Adults, Admitted to a Non-ICU Department With >24 h of Systemic Antibiotics Because of a Suspected Bacterial Infection
31	A current local antibiotic guideline should be present in the hospital and an evaluation whether an update should be considered should be done every 3 y.		
32	Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.		

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

DISCUSSION

To our knowledge, this is the first study that used the RAND modified Delphi method to systematically develop a concise set of generic QIs defining appropriate antibiotic use in the treatment of all bacterial infections in adult patients hospitalized at non-ICU departments.

Antibiotic stewardship programs are increasingly being implemented in hospitals to optimize antibiotic use. Most important in these programs tends to be the provision of guidelines and instructions for prescribers, but this alone will not be sufficient to bring about change and improvement of antibiotic use [17]. Our set of generic QIs provides important parameters that can be used to measure the various steps in the process of antibiotic use on patient level—as described with our QIs—along the entire antibiotic pathway. These QIs enable stewardship teams to determine for which steps along the antibiotic pathway there is room for improvement, and to set priorities for targeted improvement actions in their specific hospital. The effectiveness of these actions can, again, be measured using the QIs. In this manner, a quality system can be introduced in hospitals to continuously self-monitor and improve the appropriateness of antibiotic use. Of course, our QIs can also be used by groups of hospitals for benchmarking inpatient hospital QI performance to further improve antibiotic use.

The generic set contains 11 QIs describing appropriate antibiotic use, from start to discontinuation of antibiotics. All indicators received a high score in the first questionnaire round. We also asked the panel members to rank this complete set, to see if there was a hierarchy within this set of QIs. The results shows that taking cultures, prescribing empirical therapy according to the guideline, and streamlining antibiotic therapy received the highest scores.

Our study has several strengths. First, the set of QIs was specifically designed for hospitalized patients. The European Surveillance of Antimicrobial Consumption developed QIs to measure appropriate outpatient antibiotic use in Europe [12, 18]. However, this set was not designed to measure the appropriateness of antibiotic use in individual patients. Second, we used the Delphi procedure, where scientific evidence is combined with expert opinion, which is well known and described in other studies [10, 11, 19]. The application of this systematic and rigorous consensus method for indicator development resulted in indicators with high content validity. Recently, 2 reviews were published on methods for developing QIs, and the use and reporting of the Delphi method. Both reviews reported a substantial variety among studies [20, 21]. Boulkedid and colleagues developed practical guidelines for using the RAND modified Delphi technique, and our procedure is consistent with these guidelines [20].

Another strength was the multidisciplinary expert panel, which was an international panel in which all the main specialities involved in antibiotic treatment were represented. This resulted in a diversity of practices and opinions, which strengthens the results of the Delphi procedure. In addition, both the scientific literature search and the expert panel were international. We therefore believe these QIs represent a valid set that can be used internationally.

This study also has some limitations. Twenty-nine percent of the experts attended the panel meeting. All attendees were Dutch because of logistical reasons. Nevertheless, the response rates of the first and second questionnaire were 94% and 100%, respectively, which is very high. An extensive summary with regard to the results from the consensus meeting was sent to all panel members, and they were asked to give their final remarks and approval for the added and rephrased potential QIs. Because the entire panel returned the second questionnaire, we believe that an incomplete attendance did not undermine the validity of the results.

Another potential limitation was that none of the QIs had "grade 1" evidence (Tables 1–3). This is, however, exactly the

reason we used the Delphi method, as it systematically combines evidence and consensus of experts, which enables the assessment of a broader range of topics than would otherwise be possible.

In conclusion, the applicability of QIs should always be tested in practice first, as registration of data is different in every country, which affects the feasibility, validity, and reliability of data collection [11]. Also, within a country, registration may vary between and sometimes even within clinical settings. We therefore strongly advise to first test the clinimetric properties of the QIs to discriminate between indicators that are feasible, valid, and reliable in a specific setting and those that are not. Such a test will also facilitate acceptance of the measures. For example, at this moment we are testing the clinimetric properties of our QIs in approximately 1800 hospitalized patients, in 22 Dutch hospitals. Similarly, the feasibility, validity, and reliability of the QIs should be tested in other countries/states, to check whether our antibiotic stewardship QIs are also applicable and comparable internationally.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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References

1. World Health Organization. Global strategy for containment of antimicrobial resistance. Geneva, Switzerland: WHO, **2011**.
2. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **2007**; 44:159–77.
3. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ **1999**; 318:527–30.
4. Arnold FW, LaJoie AS, Brock GN, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med **2009**; 169:1515–24.
5. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Impact of guideline-concordant antibiotics and macrolide/beta-lactam combinations in 3203 patients hospitalized with pneumonia: prospective cohort study. Clin Microbiol Infect **2013**; 19:257–64.
6. Larson EL, Quiros D, Giblin T, Lin S. Relationship of antimicrobial control policies and hospital and infection control characteristics to antimicrobial resistance rates. Am J Crit Care **2007**; 16:110–20.
7. Lee SS, Kim Y, Chung DR. Impact of discordant empirical therapy on outcome of community-acquired bacteremic acute pyelonephritis. J Infect **2011**; 62:159–64.
8. Menendez R, Torres A, Reyes S, et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. Eur Respir J **2012**; 39:156–62.
9. Campbell SM, Braspenning J, Hutchinson A, Marshall MN. Research methods used in developing and applying quality indicators in primary care. BMJ **2003**; 326:816–9.
10. Hermanides HS, Hulscher ME, Schouten JA, Prins JM, Geerlings SE. Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: a first step to measure and improve care. Clin Infect Dis **2008**; 46:703–11.
11. Schouten JA, Hulscher ME, Wollersheim H, et al. Quality of antibiotic use for lower respiratory tract infections at hospitals: (how) can we measure it? Clin Infect Dis **2005**; 41:450–60.
12. Coenen S, Ferech M, Haaijer-Ruskamp FM, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. Qual Saf Health Care **2007**; 16:440–5.
13. Campbell SM, Braspenning J, Hutchinson A, Marshall M. Research methods used in developing and applying quality indicators in primary care. Qual Saf Health Care **2002**; 11:358–64.
14. Fitch K, Bernstein SJ, Aguilar MS, et al. RAND/UCLA appropriateness method user's manual. **2001**.
15. Campbell SM, Cantrill JA, Roberts D. Prescribing indicators for UK general practice: Delphi consultation study. BMJ **2000**; 321:425–8.
16. van den Bosch CM, Hulscher ME, Natsch S, Gyssens IC, Prins JM, Geerlings SE. Development of quality indicators for antimicrobial treatment in adults with sepsis. BMC Infect Dis **2014**; 14:345.
17. Charani E, Cooke J, Holmes A. Antibiotic stewardship programmes—what's missing? J Antimicrob Chemother **2010**; 65:2275–7.
18. Adriaenssens N, Coenen S, Versporten A, Muller A, Vankerckhoven V, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. J Antimicrob Chemother **2011**; 66(suppl 6):vi71–7.
19. van Hulst LT, Fransen J, den Broeder AA, Grol R, van Riel PL, Hulscher ME. Development of quality indicators for monitoring of the disease course in rheumatoid arthritis. Ann Rheum Dis **2009**; 68:1805–10.
20. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One **2011**; 6:e20476.
21. Kotter T, Blozik E, Scherer M. Methods for the guideline-based development of quality indicators—a systematic review. Implement Sci **2012**; 7:21.