ORIGINAL RESEARCH

Development and Application of a Reference Manual for Diagnosis and Rational Use of Antimicrobial Agents for Outpatient Primary Care (Digestive System Part): A Delphi Study

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Purpose: To establish a concise and easy-to-understand reference manual for outpatient primary care providers, promoting correct diagnosis of digestive system diseases and rational antimicrobial use.

Methods: The establishment of the manual encompassed two processes: the development of a draft manual and the validation of the manual. The development process was based on a literature review and expert discussion. The manual comprises portions for disease diagnosis and rationality of antimicrobial use. The validation process employed a two-round Delphi technique, collecting consensus through paper-based or mail-based communications. The response of the Delphi group was assessed by the level of authority and commitment of the panelists and the degree of agreement among them. Furthermore, the manual was preliminarily applied among primary care physicians.

Results: A total of 29 panelists completed the Delphi working process. They were authoritative in their professional fields with authority coefficients of 0.813 and 0.818 for the two portions of the manual, respectively. The level of commitment of the panelists was measured by response rates, which were 100.00% and 96.67% for Round 1 and 2. After two rounds, a consensus was achieved with the consensus rates for the two portions of the manual being greater than 65% and 70%, respectively. Kendall W-tests had P-values < 0.001 in both rounds. This reference manual provides 200 diagnostic indicators for 29 common digestive diseases and recommendations for the rational use of antimicrobial agents for 13 categories of digestive diseases. The primary care physicians who used the reference manual reported high satisfaction and frequent usage.

Conclusion: Based on a collective consensus of professionals, a reference manual has been established, to provide a concise and easy-to-understand guide specifically for physicians and pharmacists in outpatient primary care. It could facilitate rapid learning to improve the accuracy of diagnosis and treatment for digestive disorders.

Keywords: primary health care, digestive system, diagnosis, antimicrobial agents, rational drug use, Delphi technique

Introduction

According to the World Health Organization (WHO)[1] and the Global Burden of Disease (GBD) study published in the Lancet,[2] approximately 2.05 billion people in the world suffer from digestive diseases, with a mortality rate as high as

5433

31.8%. This highlights the urgent need for effective diagnosis and treatment of digestive system disorders. However, it has been reported that the diagnosis of digestive disorders is often delayed (6.4 months on average after clinical onset) and incorrectly diagnosed.[3] This might be attributed to the large number of digestive disease sub-types and the absence of reliable diagnostic markers in the early stages of the diseases.[4]

Incorrect treatment of diseases is also common in primary care outpatient settings.[5] In our previous study in China, primary care physicians prescribed antimicrobial medications for digestive diseases purely based on patients' wishes or their arbitrary experiences: up to 89.9% of prescriptions for digestive diseases were irrationally used or abused.[6] In the context of the digestive system, antibacterial agents are primarily employed to address bacterial infections, while viral infections do not necessitate their use. For instance, when dealing with infectious diarrhea caused by a virus, anti-microbial therapy is not required.[7] Antimicrobial agent abuse is a significant cause of concern for antimicrobial resistance.[8] Taking *Helicobacter pylori* infection as an example, it could lead to various conditions, such as chronic gastritis, duodenitis, and stomach ulcers. It is important to note that the irrational use of antimicrobial medications will exacerbate this infection by fostering resistance, ultimately leading to a reduced eradication rate of *Helicobacter pylori* and prolonging the infection.[9]

According to Health Statistics Yearbooks of China[10] and Guizhou[11] (a typical poor mountainous province in China) over the last three years, primary care staff are in short supply (only 0.39 medical and nursing personnel per 1000 population). The vast majority (85%) of them have only a junior college education or below with insufficient knowledge and expertise.

Currently, although there are numerous clinical practice guidelines and guiding principles available for health workers to use, they are generally somewhat broad and not specially tailored for primary care settings. A PubMed search with the Title/Abstract "primary care" and "China" yielded 1016 studies, and another search with "primary care", "digestive", and "China" yielded only 10 studies, until July 18, 2023. It may be inferred that digestive diseases in primary care in China has not received enough attention. This study is necessary, because a valid and reliable reference manual that is easy to understand may promote primary healthcare providers to correctly diagnose and rationally use antimicrobial agents. In this case, the Delphi technique is useful because it helps discover issues in clinical practices that a group of experts believes to be important. It is widely utilized and accepted in medical research.[12]

Our research team had previously established a reference manual for the diagnosis and rational use of antimicrobial agents for respiratory illnesses, which is currently well used in outpatient primary care practices in China.[13] The present study targets diseases of the digestive system. The objective of this study is to establish a reference manual for outpatient primary care, which is concise and easy-to-understand, for the diagnosis of common digestive diseases and the rational use of antimicrobial agents, through a collective consensus of professionals.
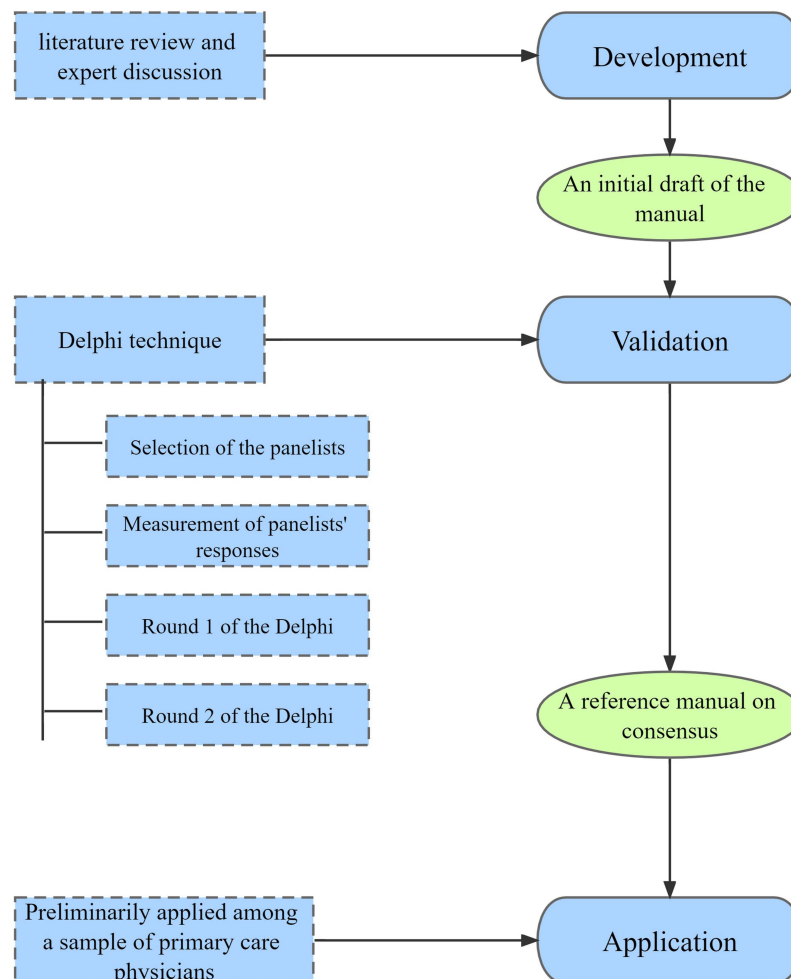
Materials and Methods
Study Design
In this study, the *Reference Manual for Diagnosis and Rational Use of Antimicrobial Agents for Outpatient Primary Care (Digestive System Part)* (hereinafter referred to as the "reference manual") was established. *This manual is divided into two independent portions: the diagnosis of common digestive diseases (hereinafter referred to as* "disease diagnosis"*) and the rational use of antimicrobial agents (hereinafter referred to as* "rationality of antimicrobial use"*).*

The methodology for the manual establishment encompassed two processes: the development of a draft manual and the validation of the manual. The development process was based on a literature review and expert discussion. The Delphi technique was systematically and rigorously performed to validate the reference manual, following the Delphi guidelines for the health field,[14] with a specific focus on primary health care.[15] Furthermore, the manual was preliminarily applied among a sample of primary care physicians. A diagram illustrating the methods of this study is presented in Figure 1.

Development of the Reference Manual
A review of authoritative medical textbooks, guidelines, and related studies included: 1) *Diagnostics* and *Internal Medicine* published by People's Medical Publishing House of China, 2) *Guiding Principle of Clinical Use of*

Figure 1 Diagram illustrating the methods of this study.

Antibiotics by the National Health Commission of the People's Republic of China,[7] summarized in Supplementary Materials 1, 3) *Guidelines for use of antibiotics*[16] by the United States Centers for Disease Control and Prevention (CDC), and 4) our previous research.[6,17] They all served as the foundation for the development of the initial draft of the manual. However, current guidelines are evidence-based, with a methodology that locates the best research evidence through systematic literature reviews, to address clinical questions.[18] As we mentioned above, there is not much evidence from primary care, as work burnout is prevalent among primary care physicians, who indicate that there is no spare time for research.[19] Currently, there are no guidelines specifically applicable to primary care settings. In the following step, a meeting of experts from the government and hospitals (the Health Commissions of Guizhou, Guangxi, and Yunnan provinces, the Second Affiliated Hospital of Kunming Medical University, the Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, and the People's Hospital of Guizhou Province) thoroughly discussed issues in the diagnosis and treatment of digestive diseases in outpatient primary care practices that had been neglected in the literature. They discovered that current international or national guidelines are often specialized in nature, which can be challenging for primary care providers to comprehend. Therefore, there is a need for a concise and easily understandable manual for users in primary care. Subsequently, an initial draft of the manual was prepared, which would be later distributed to

Delphi panelists. A pilot test was conducted among the research members prior to the implementation of the Delphi working process, as advised by the Delphi guidelines.[14]

Validation of the Reference Manual

Selection of the Panelists

The Delphi technique entails persons with a deep understanding of the topic under research, defined as "panelists" in the current study. Separate eligibility criteria were determined for the two portions of the reference manual. A purposive sampling was employed. Each panelist was purposefully selected based on their knowledge or experience related to our research topic.

The following eligibility criteria were used for the disease diagnosis portion: 1) having experience working or assisting in primary care practices; 2) possessing over 10 years of experience in clinical diagnosis of digestive system diseases; 3) being interested in this study and willing to participate; 4) specialists holding an associate senior title or higher.

The following eligibility criteria were used to select panelists for the rationality of antimicrobial use portion: 1) having experience working or assisting in primary care practices; 2) possessing over 10 years of experience in clinical prescription or pharmaceutical research on digestive diseases; 3) being interested in this study and willing to participate; 4) specialists holding an associate senior title or higher.

The panelists involved in this study were all specialists with experience in primary care settings. China is currently developing and strengthening an integrated healthcare system that facilitates collaboration between primary care and higher hospitals.[20] This requires the transfer of specialists to primary care institutions to provide guidance and support to primary care.

Measurement of the Panelists' Responses

In the initial draft of the manual, the common digestive system disorders among outpatients in primary care, including diseases from the mouth to the anus,[21] were investigated and enumerated according to the International Classification of Diseases (ICD-10) code, which is familiar in primary care settings in China. In the disease diagnosis portion of the manual, items were formed by standardizing the diagnosis of the above-mentioned diseases in terms of symptoms, signs, and ancillary tests. In the rationality of antimicrobial use portion, the items were evaluated for 13 categories of digestive diseases, assessing the rationality of antimicrobial use in each case. Common categories of antimicrobial agents used in outpatient primary care practices were listed, including *Penicillins, Cephalosporins, Macrolides, Quinolones, Lincosamides, Nitroimidazoles, and Aminoglycosides*.[6,22] We used broad categories of antimicrobial agents instead of subcategories or single molecules because primary care institutions in China are often confined to the use of the unrestricted class of antimicrobial agents. This is a result of the implementation of antimicrobial stewardship policies in China, which prioritize safety, minimization of the risk of antimicrobial resistance, best practice prescribing, and public health interests. Similar antimicrobial restrictions have been established in many other countries.[23] According to the *National Catalog for Clinical Application of Antimicrobial Agents* by the National Health Commission of the People's Republic of China, antimicrobial agents are classified into three classes, unrestricted, restricted, and special. The catalog is detailed in Supplementary Material 2.

All items in both portions of the draft manual were evaluated by the Delphi panelists based on clinical guidelines, their diagnosis or prescription experience, and the features of primary care settings. A Likert scale was used for the quantitative evaluation, ranging from 4 to 1: score 4 (very high diagnostic value, indicating preferred medication, optimal), score 3 (high diagnostic value, indicating antimicrobials can be used or substituted, acceptable but not optimal), score 2 (average diagnostic value, indicating no need to use, e.g., prescribing antimicrobials to prevent viral infections), score 1 (low diagnostic value, indicating incorrect spectrum of antimicrobials based on pharmacological actions, antibacterial spectrum, adverse drug reactions, and a table titled "Principles of empirical antibiotic treatment for various bacterial infections" from the guidelines[7,16] [see Supplementary Table 1]. For instance, when diagnosing acute tonsillitis and acute pharyngitis, the main pathogens are *Group A hemolytic streptococcus*, with a few being *Group C or G hemolytic streptococcus*. In such cases, if a particular panelist

prefers *Penicillins* for empirical treatment with antimicrobials, *Penicillins* would be given a score of 4 (indicating preferred medication, optimal); if he or she uses *Cephalosporins* as a possible alternative, *Cephalosporins* would be given a score of 3 (indicating antimicrobials can be used or substituted, acceptable but not optimal). In addition, in order to encourage the panelists to donate as many comments as possible, each rating was followed by a space where they could offer their comments.

Iterative Working Process of the Delphi

The Delphi is an iterative working process that aims to combine opinions into a group consensus. It is important to pre-define the term "consensus",[14] which in the context of this study refers to the group response reaching stability without further changes.

From August 2020 to February 2021, the Delphi process was conducted through paper-based or mail-based communications. In the first round of the Delphi, after the responses had been returned, the research team synthesized the responses in a summary feedback form (statistical evaluation of the group response) without including any information from the researchers.[24] In the second round, the panelists had the opportunity to change their opinions based on the feedback from the previous round that was provided anonymously to the panelists. Our working team continued to present the analytical results of the previous round to the panelists and solicit feedback, until a consensus was reached.[25] After discussion among the researchers, this report was finally formed.

Statistical Evaluation of the Group Response

EpiData software (version 3.1) was used to double input panelist scores from paper responses, and SPSS software (version 23, IBM Corp) was used for statistical analysis. Each item of the manual was described by the median for central tendency and the coefficient of variation (CV) for dispersion.

The response of the group was assessed by the level of authority and commitment of the panelists, as well as the degree of agreement among them. First, the level of authority of the panelists was measured by the authority coefficient (Cr), self-reported by the panelists.[26] It is the average of the familiarity with the research topic (Cs) and the judgment basis (Ca). The calculation formula is as follows:

$$Cr = \frac{(Ca + Cs)}{2}$$

It is generally believed that $Cr \geq 0.7$ indicates a high level of authority.[26] Second, the level of commitment of the panelists was measured based on the response rate. Sumsion (1998) suggested a minimum response rate of 70% for each round.[27] Third, the degree of agreement among the panelists was expressed by the consensus rate, and the Kendall *W* was used for the test. The consensus rate is the percentage of the panelists that have come to an agreement. If the result of the Kendall *W*-test was significant ($P < 0.05$), the panelists' assessments were considered to have a high degree of consensus.

Application of the Reference Manual

The Digestive System Part of the reference manual reported in this study, was combined with other parts developed by our research team for various systemic disorders to form a brochure. This brochure was then distributed to a sample of primary care physicians for their use and evaluation.

A cluster sampling method was used to select samples from 39 primary care institutions. The sampling frame was the list of primary care institutions from the database of the Information Center of the Guizhou Provincial Health Commission, with the eligibility criteria of 1) using the Health Information System of the Information Center of the Guizhou Provincial Health Commission, and 2) having outpatient physicians who had worked in primary care institutions for more than one year.

After the sample of physicians had used the reference manual for more than three months, we used an electronic questionnaire (see Supplementary Material 3) to investigate their manual utilization patterns, satisfaction, and suggestions. The results were presented using percentages.

Results

Characteristics of the Panelists

A total of 30 experts were confirmed eligible and invited to participate. Since one panelist withdrew before the second round, 29 panelists committed to this Delphi working process. The comments of the withdrawal panelist were analyzed and carefully considered in accordance with the Delphi guidelines.[15] Of those who participated, 10 were male and 19 were female. There were 12 clinical doctors, including specialists in the fields of diagnostics or digestive diseases, 16 clinical pharmacists, including specialists in the fields of antimicrobial therapy, digestive diseases, or prescription review. Additionally, one pharmacological laboratory scientist was involved. All had more than 10 years of experience working in their professional fields. More importantly, 4 panelists had ≥ 5 years of primary care experience, 12 panelists had 3~4 years, and 13 panelists had 1~2 years. The characteristics of the panelists are shown in Table 1.

Level of Authority of the Panelists

The level of authority of the panelists was calculated and presented in Table 2. The authority coefficients for either portion of the manual were greater than 0.70.

Table 1 Characteristics of the Panelists

Characteristic	Disease Diagnosis Portion (n=12)	Rationality of Antimicrobial Use Portion (n=17)
	N (%)	N (%)
Working years		
10~19	3 (25.00)	7 (41.18)
20~29	5 (41.67)	8 (47.06)
≥30	4 (33.33)	2 (11.76)
Title		
Professor	2 (16.67)	7 (41.18)
Associate Professor	10 (83.33)	10 (58.82)
Education		
Doctor	0 (0.00)	4 (23.53)
Master	9 (75.00)	7 (41.18)
Undergraduate	3 (25.00)	6 (35.29)
Occupation		
Clinician / Pharmacist	12 (100.00)	16 (94.11)
Scholar	0 (0.00)	1 (5.89)
Years of experience in primary care		
1~2	5 (41.67)	8 (47.06)
3~4	5 (41.67)	7 (41.18)
≥ 5	2 (16.66)	2 (11.76)

Table 2 Authority Coefficients for Either Portion of the Manual

Portion	Ca	Cs	Cr
Disease diagnosis	0.93	0.70	0.81
Rationality of antimicrobial use	0.91	0.72	0.82

Notes: Ca, judgment basis; Cs, familiarity with the research topic; Cr, authority coefficient.

Level of Commitment

It took two rounds to reach a collective consensus in this study. Totally, 44 free-text comments were contributed by the panel. Table 3 displays the response rates of the Delphi panel.

Degree of Agreement

In the second round, the consensus rates for either portion of the disease diagnosis or the rationality of antimicrobial use in the manual were more than 65% and 70%, with Kendall W being 0.60 ($P < 0.001$) and 0.71 ($P < 0.001$), respectively. After two rounds of evaluation, the stability of the results led the Delphi work to a consensus.

Reference Manual

The cover, table of contents, and example pages of the reference manual are illustrated in Figure 2.

Disease Diagnosis Portion

In Round 1 and 2, a total of 220 diagnostic items were assessed for 29 common digestive system diseases in outpatient primary care. Items that received the lowest diagnostic value assessment (scored 1 on the Likert scale of 1 to 4) from all panelists were removed. The remaining 200 items are presented in the reference manual. Due to the limited space of the manuscript, 167 items that received the highest diagnostic value assessment (scored a median of 4 on the Likert scale of 1 to 4) in the collective consensus were listed as diagnostic indicators in Table 4.

Rationality of Antimicrobial Use Portion

The recommendations for the selection of antimicrobial agents in outpatient primary care practices for 13 categories of common digestive system disorders are given in Table 5.

Application of the Reference Manual

A total of 160 physicians, who had used the reference manual for at least three months, participated in our survey, providing feedback into their utilization patterns, satisfaction levels, and suggestions. The findings indicated that more than 90% of them used the manual 2–3 times per week, 88.13% were satisfied with it, more than 95% considered it useful in improving their knowledge and expertise, and 98.13% would recommend it to other outpatient physicians. It is worth noting that 100% of physicians believed this manual was applicable to primary care settings.

Discussion
Findings of the Study

The Delphi technique is widely used and accepted in medical research to establish group consensus and contribute to successful decision-making, particularly for topics that the traditional evidence-based medicine paradigm could not or

Table 3 Response Rates for Round 1 and 2

Round	Draft Manual Distributed	Responses Returned	Response Rate	Effective Response Rate
1	30	30	100.00%	100.00%
2	30	29	96.67%	100.00%

(A) Cover

Diagnosis and Rational Use of Antimicrobial Agents for Outpatient Primary Care

Reference Manual

(B) Table of contents

Table of contents

(C) Recommendation table for diagnosis of common digestive diseases in primary care

ICD-10	name of disease			Diagnostic item	Diagnostic value
K05.105	Gingivitis	Symptom	1	Gums bleed when brush teeth or bite on something hard (bright red).	3
			2	Gingiva local itching, swelling, discomfort and bad breath.	3
		Sign	1	Gingival edges and nipples are bloodshot, swollen and shiny. The gums are bright red or deep red and bleed when touched.	4
			2	Free gingival and gingival papilla are bright red or dark red, hyperemia can spread to the attached gingival.	2
			3	Gingival material is soft and fragile, lack of elasticity.	2
			4	Gingival sulcus probing was more than 3cm, gingival sulcus can bleed lightly, exudate increased in gingival sulci.	2
K05.301	Periodontitis	Symptom	1	Gingiva redness, swelling, bleeding (dark red).	4
			2	Gingival abscess, periodontal pocket formation (true periodontal pocket).	2
			3	Loose teeth, weak chewing.	2
		Sign	1	The gums recede and are exposed.	4
			2	It is attached and can penetrate into the cementum enamel.	3
			3	Peridental abscess.	2
		Auxiliary test	1	X-ray examination: periodontal space widened, alveolar bone was horizontal absorption.	2
K08.861	Toothache	Symptom	2	Mainly toothache, or sometimes pain sometimes stop, when cold or hot ...	4

(D) Recommendation table for the selection of antimicrobial agents for 13 categories of digestive diseases in primary care

Preferred medication, optimal (P)
Acceptable, an alternative (A)
No need to use (N)
Wrong spectrum (W)

ICD-10 code	Category of disease	Penicillins	Cephalosporins	Macrolides	Quinolones	Lincosamides	Nitroimidazoles	Aminoglycosides
3. Digestive system diseases								
K04	Diseases of pulp and periapical tissues	P	A	A	A	A	P	W
K05	Gingivitis and periodontal diseases	P	A	A	A	W	P	W
K08	Other disorders of teeth and supporting structures	N	N	N	N	N	N	N
K12	Stomatitis and related lesions	A	A	A	W	W	A	W
K21	Gastro-oesophageal reflux disease	N	N	N	N	N	N	N
K25	Gastric ulcer	P	W	A	A	W	A	W
K29	Gastritis and duodenitis	P	W	A	A	W	A	W
K35	Acute appendicitis	A	P	W	A	A	A	A
K36	Other appendicitis	P	P	A	P	A	P	W

Figure 2 Cover, table of contents, and example pages of the reference manual.
Notes: (**A**) Cover of the reference manual; (**B**) Table of contents of the reference manual; (**C**) Example page of the disease diagnosis portion of the reference manual providing diagnostic indicators for common digestive diseases; (**D**) Example page of the rationality of antimicrobial use portion of the reference manual providing recommendations for the selection of antimicrobial agents in outpatient primary care practices for common digestive system disorders.

does not apply to solve.[14,15] The selection of the panel is considered to be crucial for a Delphi study.[15] This study involved 29 panelists with more than 10 years of work experience who have extensive clinical knowledge, expertise, or research in the fields of diagnostics or antimicrobial therapy for common digestive system diseases, and more importantly, experience in primary care work or assistance. The results of high authority coefficients in this study imply that the panelists are authoritative. The purposive sampling with the eligibility criterion of having experience in primary care work or assistance practices suggests that they were selected for our endeavor to improve primary care practices. Furthermore, in both rounds of the Delphi working process, high response rates, that is active commitment, ensured the study's validity.[28] Finally, both the results of consensus rates and Kendall W-tests meet the criteria by the Delphi guidelines.[14,15] Although the consensus rates in this study are not as high as over 80%, they met the stopping criterion—stability of responses—as specified by the present Delphi procedure. It has been explained that an artificially boosted consensus could distort the findings of the study, a phenomenon called "consensus bias".[15] In fact, for all items in the current study, more than half of the panelists reached a consensus, which we did not consider a low consensus rate, hence we did not remove any items because of panelist disagreement. Collectively, all of the statistical evaluations of the group response discussed above reveal the validity and reliability of the present Delphi study.

According to the WHO, 8 out of the 12 bacteria that are the most threatening to human health infect the human digestive system.[29] Digestive system diseases are widespread and occur often in primary care settings. Through the collective wisdom of the panelists, our study established a reference manual for digestive disorders for outpatient primary care. In the disease diagnosis portion of the manual, a total of 200 diagnostic items (standardized by symptoms, signs, and auxiliary tests) are provided for 29 common digestive disorders for primary care settings. Among them, 167 items with the highest diagnostic value (received a median score of 4) were the diagnostic indicators recommended by the

Table 4 Diagnostic Indicators of Common Digestive Diseases in Outpatient Primary Care: Consensus Among Panelists

Disease Classification				Diagnostic Item[a]	Median (CV/CR)[b]
K04 Diseases of pulp and periapical tissues					
K04.002	Acute pulpitis	Symptom	1	Severe spontaneous pain; hot and cold stimuli aggravate the pain; the pain was exacerbated at night.	4(0.10/83.30)
		Sign	1	On examination, there were deep caries holes with obvious pain, and there were perforating holes.	4(0.13/66.70)
			2	The affected tooth is extremely sensitive to temperature tests.	4(0.12/75.00)
K04.003	Chronic pulpitis	Symptom	1	Hot and cold irritates pain.	4(0.12/75.00)
			2	Food embedded pain.	4(0.10/83.30)
		Auxiliary test	1	On pulp vitality test, the irritation point was higher than normal. Percussion may be negative. However, when the periapical tissue is affected, percussion can also be positive.	4(0.17/83.30)
K04.401 Acute apical periodontitis		Symptom	1	The teeth elongate and emerge. When teeth closed, there is early contact or discomfort. There is mild pain confined to the root of the tooth.	4(0.12/75.00)
		Sign	1	Local gingival red oedema, tenderness.	4(0.12/75.00)
		Auxiliary test	1	X-ray: (1) Negative or with widened periodontal space; (2) Acute apical abscess: if it is primary, apical bone has no obvious destruction, trabecular bone is fuzzy, hard plate is not clear.	4(0.12/75.00)
K05 Gingivitis and periodontal diseases					
K05.105	Gingivitis	Sign	1	Gingival edges and nipples are bloodshot, swollen, and shiny. The gums are bright red or deep red and bleed when touched.	4(0.18/75.00)
K05.301	Periodontitis	Symptom	1	Gingiva redness, swelling, bleeding (dark red).	4(0.18/75.00)
		Sign	1	The gums recede and are exposed.	4(0.22/75.00)
K08 Other disorders of teeth and supporting structures					
K08.851	Toothache	Symptom	1	Mainly toothache, or sometimes pain sometimes stop, when cold or hot stimulation pain.	4(0.10/83.30)

(*Continued*)

Table 4 (Continued).

Disease Classification				Diagnostic Item[a]	Median (CV/CR)[b]
K21 Gastro-esophageal reflux disease					
K21.001	Reflux esophagitis	Symptom	1	Reflux and heartburn.	4(0.10/83.30)
		Auxiliary test	1	Gastroscopy: (1) Classification of reflux esophagitis: Normal: Esophageal mucosa was not damaged; A class: one or more esophageal mucosa was damaged, and the length diameter was < 5mm; B class: one or more esophageal mucosa was damaged, with length > 5mm, but no fused lesions; C class: the esophageal mucosa was damaged and fused, but less than 75% of the periesophageal diameter; D class: the esophageal mucosa was damaged and fused, involving at least 75% of the esophageal circumference. (2) Non erosive reflux disease (NRED): negative.	4(0.10/83.30)
K25 Gastric ulcer					
K25.903	Gastric ulcer	Symptom	1	Pain in the upper abdomen. It may also be present in the left upper abdomen or behind the sternal xiphoid process. It often presents dull pain, dull pain, distension pain, burning pain. Most of them appear within 1 hour after meals and relieve within 1–2 hours.	4(0.12/75.00)
		Auxiliary test	1	Gastroscopy: Ulcers can be divided into three stages: (1) Active stage: the base of the ulcer is covered with white or yellow-white thick moss, and the surrounding mucosa is congested and oedema (A1), or the surrounding mucosa is congested and oedema begins to fade, and the red halo formed by the regenerated epithelium appears around (A2); (2) Healing stage: the ulcer shrinks and becomes shallow, the moss becomes thin, and the red halo formed by the regenerated epithelium around the ulcer is surrounded by the ulcer, and the mucosal fold is concentrated toward the ulcer (H1), or the ulcer surface is almost covered by the regenerated epithelium, and the mucosal fold is more concentrated toward the ulcer (H2); (3) Scar stage: the white moss disappears at the base of the ulcer, presenting red scar (S1), and finally turning into white scar (S2).	4(0.07/91.70)
			2	Hp testing +	4(0.13/66.70)
K29 Gastritis and duodenitis					
K29.101	Acute gastritis	Symptom	1	Often upper abdominal pain, distension.	4(0.18/75.00)
		Auxiliary test	1	Endoscopic examination: the gastric mucosa was obviously congested and edematous, sometimes with erosion and bleeding spots. The mucosal surface was covered with sticky inflammatory exudates and mucus.	4(0.10/83.30)
K29.303 Chronic superficial gastritis		Symptom	1	Abdominal pain and distension.	4(0.12/75.00)
		Auxiliary test	1	Gastroscopy: gastric mucosa congestion, oedema, red and white alternating, can be accompanied by erosion bleeding or bile reflux.	4(0.07/91.70)
			2	Hp testing: the positive rate of Hp infection is up to 70~90%. Gastric mucosa tissue can be taken by gastroscopy and the antibody of Helicobacter pylori can also be detected in the blood of patients.	4(0.10/83.30)

K29.401 Chronic atrophic gastritis	Auxiliary test	1	Gastroscopy: (1) the color of gastric mucosa becomes faint; (2) submucosal blood vessels were permeable; (3) mucosal folds were small or even disappeared; (4) when atrophic gastritis is accompanied by excessive glandular neck hyperplasia or intestinal metaplasia, the mucosal surface is rough and uneven, granular or nodular, sometimes the formation of pseudo polyps can be seen, and the characteristics of submucosal blood vessels are often hidden; (5) increased fragility of atrophic mucosa, easy bleeding, and erosion foci; (6) atrophic gastritis can be accompanied by the manifestations of chronic superficial gastritis, such as hyperemia and erythema, adhesion of mucus, and enhanced reflection of light.	4(0.07/91.70)
		2	Pathological examination: (1) inherent glandular atrophy in gastric mucosa; (2) metaplasia; (3) hyperplasia; (4) carcinogenesis.	4(0.17/83.30)
K29.502	Chronic gastritis	Symptom	1	Most patients have no obvious symptoms. If symptoms are present, they are mostly nonspecific. Can show is in upper abdomen unwell, full distension, dull ache, burning kind ache to wait also can show appetite lack, belching, pantothenic acid, nausea wait for dyspeptic symptom.	4(0.10/83.30)
			2	Critical illness stress: Patients may suddenly hematemesis and/or melena as the first symptoms.	4(0.12/75.00)
		Sign	1	Signs are not obvious, sometimes the upper abdomen light tenderness.	4(0.07/91.70)
		Auxiliary test	1	Hp testing: the exhaled breath of the patient is tested for the presence of labelled C-13, which indicates the presence of Helicobacter pylori.	4(0.07/91.70)
			2	Gastroscopy, mucosal congestion, swelling and erosion; Shrinking. +	4(0.12/75.00)
K29.802	Duodenitis	Symptom	1	Upper abdominal pain.	4(0.12/75.00)
		Auxiliary test	1	Endoscopic examination: (1) superficial type: mucosal congestion and oedema, enhanced reflection, red and white, mainly red; (2) bleeding and erosion type: mucosa redness, punctate and flake erosion or bleeding foci; (3) atrophic type: the mucosa becomes thin and pale, mainly white, and submucosal blood vessels are exposed; (4) hyperplastic type: coarse and uneven mucosa or fine granular nodular changes.	4(0.13/66.70)
			2	Hp testing +	4(0.18/75.00)

(*Continued*)

Table 4 (Continued).

Disease Classification				Diagnostic Item[a]	Median (CV/CR)[b]
K35 Acute appendicitis					
K35.902	Acute appendicitis	Symptom	1	Abdominal pain: The onset of abdominal pain typically begins in the upper abdomen, gradually moves to the navel, and after several hours (6–8 hours) metastasizes and becomes confined to the right lower abdomen.	4(0.07/91.70)
		Auxiliary test	1	Laboratory tests: white blood cell counts and neutrophil ratios are elevated in most patients. Urine examination generally has no positive findings, such as a small number of red blood cells in the urine, indicating that the inflammatory appendix is close to the ureter or bladder. Significant hematuria indicates the presence of a primary urological lesion.	4(0.12/75.00)
			2	Imaging examination: (1) Abdominal plain film can show cecal dilatation and liquid air plane, occasionally calcified intestinal stone and foreign body shadow, which can help to diagnose; (2) An enlarged appendix or abscess can be detected by ultrasound.	4 (0.18/75.00)
K52 Other noninfective gastroenteritis and colitis					
K52.904	Diarrhea	Symptom	1	Pus and blood or watery stool	4 (0.13/66.70)
			2	Abdominal pain	4 (0.12/75.00)
		Auxiliary test	1	Fecal examination: including fecal occult blood test, smear for white blood cells, red blood cells, undigested food, parasites and eggs, Sudan III staining for fecal fat, smear for fecal bacteria, fungi, fecal bacteria culture, etc.	4 (0.19/66.70)
			2	Blood examination.	4 (0.13/66.70)
K52.905	Acute enteritis	Symptom	1	Abdominal pain, diarrhea (yellow watery stool, foam or a small amount of mucus, severe cases with a small amount of pus and blood).	4 (0.07/91.70)
		Sign	1	There are varying degrees of tenderness in the abdomen.	4 (0.10/83.30)
		Auxiliary test	1	Routine stool: yellow watery stool with a small amount of mucus, occasionally white blood cells and pus cells. The culture can find pathogenic bacteria.	4 (0.17/83.30)
K52.906 Acute hemorrhagic enteritis		Symptom	1	Acute abdominal pain, abdominal distension, vomiting, diarrhea, blood in the stool.	4 (0.10/83.30)
		Sign	1	Relatively few. Sometimes there is abdominal distention and bowel pattern. There may be marked tenderness around the umbilicus and in the epigastrium. Early bowel sounds can be hyperactive, and then can be weakened or disappear.	4 (0.12/75.00)
		Auxiliary test	1	Stool examination: dark red or bright red in appearance, or a strong positive occult blood test, microscopically, a large number of red blood cells, occasionally detached mesentery. There may be a small or moderate amount of pus cells.	4 (0.17/83.30)

K52.908 Acute gastroenteritis	Symptom	I	(1) Mild diarrhea is generally in good condition, the stool is less than 10 times a day, yellow or yellow-green, a small amount of mucus or white soap block, fecal quality is not much, sometimes the stool is "egg soup"; (2) Severe diarrhea, several times to dozens of stools per day. Lots of watery stool, little mucus, nausea and vomiting, poor appetite. Sometimes vomit something that looks like coffee.	4 (0.10/83.30)
	Sign	I	Physical signs are not obvious. There is tenderness in the upper abdomen and around the umbilicus. No muscle tension and rebound pain. Bowel sounds more hyper.	4 (0.12/75.00)
	Auxiliary test	I	Laboratory tests: blood white blood cell count can be normal or abnormal; Routine stool examination and stool culture.	4 (0.19/66.70)
K52.909	Colitis	Symptom	I	Diarrhea (mucous stool, and pus blood stool, 3–4 times a day in mild cases, dozens of times in severe cases, the stool looks bloody).	4 (0.10/83.30)
			2	Abdominal pain.	4 (0.12/75.00)
		Auxiliary test	I	Endoscopic examination: intestinal mucosal hyperemia, oedema, granular protrusion, multiple punctate or patchy small erosion or ulcer, with mucus or yellow and white moss on the surface. Intestinal mucosa is flimsier, lens Angle has brushed easy hemorrhage, as a result of oedema and lymphoid tissue hyperplasia, visible pseudo polyp.	4 (0.10/83.30)
			2	Pathological examination of mucosa: Mucosal inflammatory cell infiltration, heterosexual epithelial cell hyperplasia, abnormal gland arrangement, epithelial fibrosis, crypt formation, etc.	4 (0.10/83.30)
K52.912	Chronic diarrhea	Symptom	I	The number of stools increased, daily defecation in more than 3 times.	4 (0.10/83.30)
			2	Loose or unformed stool, sometimes accompanied by mucus, pus, and blood. Its lasting more than two months.	4 (0.10/83.30)
		Auxiliary test	I	Fecal examination: including fecal occult blood test, smear for white blood cells, red blood cells, undigested food, parasites and eggs, Sudan III staining for fecal fat, smear for fecal bacteria, fungi, fecal bacteria culture, etc.	4 (0.18/75.00)
K61 Abscess of anal and rectal regions					
K61.001	Perirectal abscess	Symptom	I	Rectum drops distension feeling; always want to defecate; feel especially unwell when defecation.	4 (0.18/75.00)
		Sign	I	Perineum examination is mostly no abnormality; digital rectal examination can be on the rectal wall to touch swelling, tenderness, and fluctuation.	4 (0.12/75.00)
		Auxiliary test	I	Perianal skin needle puncture: pus can be extracted.	4 (0.12/75.00)

(*Continued*)

Table 4 (Continued).

Disease Classification				Diagnostic Item[a]	Median (CV/CR)[b]
K61.002	Perianal abscess	Symptom	1	Perianal persistent beating pain.	4 (0.12/75.00)
		Sign	1	The lesion is obviously red and swollen, with induration and tenderness; abscess formation can have fluctuation feeling, puncture is easy to draw out pus.	4 (0.12/75.00)
			2	Early local signs are not obvious, later appear anal side redness and swelling, double buttock asymmetry; there is deep tenderness and even fluctuation feeling in the affected side when local palpation or digital rectal examination is performed.	4(0.13/66.70)
		Auxiliary test	1	Perianal skin needle puncture: pus can be extracted.	4 (0.12/75.00)
K80 Cholelithiasis					
K80.203	Cholecystolithiasis	Sign	1	Murphy signs +	4 (0.13/66.70)
		Auxiliary test	1	Ultrasound examination: It shows the strong echogenic mass in the gallbladder, which moves with the change of body position.	4 (0.12/75.00)
K81 Cholecystitis					
K81.004	Acute cholecystitis	Symptom	1	Upper abdominal pain, progressive to paroxysmal colic, night-time attacks are common. Feasting and eating fatty food often induce upper abdominal pain. Pain radiates to the right shoulder, shoulder blade and back.	4 (0.10/83.30)
			2	Accompanied by nausea, vomiting, anorexia, constipation, and other gastrointestinal symptoms.	4(0.12/75.00)
		Sign	1	There may be tenderness in the right upper quadrant gallbladder area.	4 (0.10/83.30)
			2	Abdominal muscle tension and rebound pain; Murphy signs. +	4 (0.13/66.70)
			3	Knock pain in gallbladder area +	4 (0.13/66.70)
		Auxiliary test	1	Ultrasound examination: gallbladder enlargement and gallbladder wall thickening (>4m), "bilateral sign" was seen when there was obvious oedema, and gallstones showed strong echo followed by sound pictures.	4 (0.10/83.30)

K81.101	Chronic cholecystitis	Sign	I	There may be no positive signs or only mild tenderness in the upper abdomen.	4 (0.12/75.00)
		Auxiliary test	I	Ultrasound examination: It may show thickening of the gallbladder wall, obstruction of gallbladder emptying or gallbladder stones.	4 (0.07/91.70)
K92 Other diseases of digestive system					
K92.208 Hemorrhage of digestive tract		Symptom	I	Hematemesis and black stool.	4 (0.12/75.00)
		Auxiliary test	I	Endoscopic examination: the source of bleeding may be identified.	4 (0.07/91.70)
			2	Vomit / stool OB +	4 (0.29/75.00)
K92.206	Gastrorrhagia	Symptom	I	Chronic bleeding has no obvious symptoms.	4 (0.12/75.00)
		Sign	I	Changes in pulse and blood pressure are important indicators of blood loss. In acute gastrointestinal bleeding, the initial compensatory function of the body is increased heart rate. In the early stage of shock, blood pressure can be increased compensatively, and with the increase of blood loss, blood pressure will gradually decrease and enter the state of hemorrhagic shock.	4 (0.10/83.30)
		Auxiliary test	I	Occult blood test: Occult blood tests on vomit or black manure were strongly positive	4 (0.07/91.70)
			2	Blood routine: hemoglobin concentration, red blood cell count and hematocrit decreased.	4 (0.10/83.30)

Notes: [a]Symbol + represents the newly added items. [b]The number 4 denotes a very high diagnostic value, the number 3 denotes a high diagnostic value, the number 2 an average diagnostic value, the number I a low diagnostic value.
Abbreviations: CV, coefficient of variation; CR, consensus rate.

Table 5 Recommendations for the Selection of Antimicrobial Agents for 13 Categories of Common Digestive Disorders in Outpatient Primary Care: Consensus Among Panelists

ICD10 Code	Category of Disease	Median (Coefficient of Variation/Consensus Rate)						
		Penicillins	**Cephalosporins**	**Macrolides**	**Quinolones**	**Lincosamides**	**Nitroimidazoles**	**Aminoglycosides**
K04	Disease of pulp and periapical tissues	**P** 4 (0.10/82.4)	**A** 3 (0.12/82.4)	**A** 3 (0.11/88.2)	**A** 3 (0.14/82.4)	**A** 3 (0.35/70.6)	**P** 4 (0.10/82.4)	**W** 1 (0.57/76.5)
K05	Gingivitis and periodontal disease	**P** 4 (0.09/88.2)	**A** 3 (0.14/82.4)	**A** 3 (0.22/76.5)	**A** 3 (0.30/76.5)	**W** 1 (0.58/82.4)	**P** 4 (0.13/70.6)	**W** 1 (0.38/88.2)
K08	Other diseases of teeth and supporting structures	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)
K12	Stomatitis and related damage	**A** 3 (0.12/82.4)	**A** 3 (0.12/88.2)	**A** 3 (0.14/82.4)	**W** 1 (0.46/82.4)	**W** 1(0.54/88.2)	**A** 3 (0.08/94.1)	**W** 1 (0.23/94.1)
K21	Gastro-esophageal reflux disease	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)
K25	Gastric ulcer	**P** 4 (0.10/82.4)	**W** (0.67/70.6)	**A** 3 (0.11/88.2)	**A** 3 (0.53/70.6)	**W** 1 (0.57/76.5)	**A** 3 (0.14/76.5)	**W** (0.67/70.6)
K29	Gastritis and duodenitis	**P** 4 (0.12/76.5)	**W** (0.62/70.6)	**A** 3 (0.14/76.5)	**A** 3 (0.17/76.5)	**W** 1 (0.57/76.5)	**A** 3 (0.27/76.5)	**W** 1 (0.64/70.6)
K35	Acute appendicitis	**A** 3 (0.22/76.5)	**P** 4 (0.10/82.4)	**W** (0.33/82.4)	**A** 3 (0.35/70.6)	**A** 3 (0.15/82.4)	**A** 3 (0.14/70.6)	**A** 3 (0.25/82.4)
K52	Other noninfective gastroenteritis and colitis	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)
K61	Abscesses in the anal and rectal regions	**A** 3 (0.22/76.5)	**P** 4 (0.10/82.4)	**W** 1 (0.40/82.4)	**A** 3 (0.24/70.6)	**A** 3 (0.16/76.5)	**A** 3 (0.24/70.6)	**A** 3 (0.19/88.2)
K80	Cholelithiasis	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)
K81	Cholecystitis	**A** 3 (0.22/76.5)	**P** 4 (0.16/76.5)	**W** (0.40/82.4)	**A** 3 (0.15/82.4)	**W** 1 (0.46/82.4)	**A** 3 (0.14/82.4)	**A** 3 (0.39/70.6)
K92	Other diseases of the digestive system	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)	**N** 0 (0.00/100.0)

Abbreviations: P, Preferred medication, optimal; A, Acceptable, an alternative; N, No need to use; W, Wrong spectrum.

reference manual. Based on the panel's experience in primary care, they specifically added seven indicators that received the highest diagnostic value in the second round of the Delphi work: 1) the auxiliary test for chronic gastritis, "gastroscopy, mucosal congestion, swelling, and erosion; shrinking"; 2–3) the auxiliary test of "HP test" for duodenitis and gastric ulcer, respectively; 4) the sign of "murphy signs" for cholecystolithiasis; 5–6) the signs for acute cholecystitis, "abdominal muscle tension and rebound pain; murphy signs" and "knock pain in gallbladder area"; and 7) the auxiliary test of "vomit/stool OB" for hemorrhage of digestive tract. Regarding the portion on the rationality of antimicrobial use in the manual, recommendations on the rational use of antimicrobials for 13 categories of digestive diseases were formulated on the basis of the group consensus. It is clearly stated that antimicrobial agents are not necessary for the treatment of other diseases of teeth and supporting structures, gastro-esophageal reflux diseases, other non-infectious gastroenteritis, and colitis, cholelithiasis, and other diseases of the digestive system. Antimicrobial agents are acceptable when treating diseases of the pulp and periapical tissues, gingivitis and periodontal diseases, stomatitis and related damages, gastric ulcers, gastritis and duodenitis, acute appendicitis, abscesses in the anal and rectal regions, and cholecystitis. However, *Penicillins* and *Cephalosporins* are preferred, whereas broad-spectrum and ultra-broad-spectrum antimicrobial medicines are avoided. As mentioned above, primary care institutions are confined to the use of the unrestricted class of antimicrobial agents in China. Taking *Penicillins* as an example, the specific antimicrobials available in primary care settings include *Penicillin, Oxacillin, Amoxicillin, Ampicillin, Piperacillin, Amoxicillin/Clavulanic acid, Procaine benzylpenicillin, Penicillin V, Cloxacillin, and Carbenicillin* (see Supplementary Material 2). To exercise caution, our reference manual only provides recommendations on the rational use of broad categories of antimicrobials, since medication decisions need to be based on the patient's symptoms, signs, ancillary test results, as well as treatment history. It is still essential that primary care providers refer to clinical guidelines for the selection of subcategories or single molecule drugs to perform customized medication.

Public Health Significance for Primary Care

A *Lancet* work has reported that subpar clinical quality and diagnostic mistakes persist in primary care in China, with patients' conditions being correctly diagnosed only 26% of the time.[30] Considering the concern over high rates of inappropriate antimicrobial prescriptions, the Chinese government has been developing policies and legislation to limit antimicrobial drug abuse. However, their effectiveness in primary care settings is limited.[31] Among the primary care physicians sampled for the preliminary application of the manual in this study, the majority of them are older and busy, with little motivation to participate in systematic learning. Existing guidelines for diagnosing and treating digestive diseases are not sufficiently concise and not easy to understand, which they may find difficult to learn. The primary care physicians surveyed expressed satisfaction with the reference manual we developed, based on their usage. It is believed that this manual will aid them in rapid learning to increase disease diagnosis and treatment accuracy.

The recommendations in the *Reference Manual for Diagnosis and Rational Use of Antimicrobial Agents for Outpatient Primary Care (Digestive System Part)* are laid out in a simple-to-read format that is easy to understand. As illustrated in Figure 2, in the disease diagnosis portion of the manual, the items are presented in an easy-to-understand descending order of diagnostic values as 4, 3, and 2 (items with a diagnostic value score of 1 were excluded), so that primary care physicians can prioritize higher-valued diagnostic indicators. In the portion of the rationality of antimicrobial use of the manual, easy symbols including P (preferred medication, optimal), A (acceptable, an alternative), N (no need to use), and W (wrong spectrum) were given. Primary care physicians and pharmacists can quickly review and select the appropriate antimicrobials for a specific disease. This reference manual has public health significance for primary care. It helps primary care providers improve the correct diagnosis of diseases and rational use of antimicrobial agents by filling the research gaps in current clinical guidelines that do not address primary care.

Limitations

We cannot guarantee that the study we presented is free of bias, even though our working process followed the guidelines of the Delphi technique to reduce the possibility of systematic bias. The Delphi is a "heuristic device" for reaching a consensus among a group of professionals, which does not promise complete correctness.[14] Biases may arise from two sources in this study. Firstly, none of the panelists involved in the disease diagnosis portion had a doctoral degree.

However, these panelists are all specialists with over 10 years of experience and possess an excellent understanding of the challenges of primary care practices in China, despite the lack of doctorates. It is worth mentioning that China ranks second-to-last in the number of doctors per 1000 people, according to statistics.[32] Health workers in China carry a substantial clinical workload. In particular, specialists carry a greater clinical workload, but acquire a wealth of practical experience. Secondly, the objectivity of the assessment of the panel's authority may be compromised due to the absence of objective metrics.

The issues brought up by primary care physicians surveyed will receive ongoing attention and improvement from our research team. Moreover, the manual will be further applied among a broader group of primary care providers. In future research, with the support of this reference manual, our plan is to develop an artificial intelligence-based real-time early warning system for identifying irrational antimicrobial prescriptions, and to carry out intervention experiments in primary care settings, in hopes of achieving an effective reduction of antimicrobial resistance.

Conclusions

On the basis of a collective consensus of professionals, a *Reference Manual for Diagnosis and Rational Use of Antimicrobial Agents for Outpatient Primary Care (Digestive System Part)* was developed and validated. When applied to primary care physicians, the manual received a high level of satisfaction and recognition for its primary care applicability. It can offer recommendations to primary care physicians and pharmacists, assisting them in rapid learning to improve diagnostic and treatment accuracy for digestive diseases.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to the anonymity of a Delphi technique but are available from the corresponding author on a reasonable request.

Ethics Approval and Informed Consent

Ethical approval for the study was granted by the ethics committee of Guizhou Medical University in China, with reference number of 2019 (148). All panelists consented to participate.

Consent for Publication

All Delphi panelists consented to their personal data for publication in a scientific journal.

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Disclosure

The authors declare that they have no competing interests in this work.

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