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Clinical guidelines of UTIs in children: quality appraisal with AGREE II and recommendations analysis

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ABSTRACT

Objective To explore the current Chinese and English guidelines of urinary tract infection (UTI) in children and provide a summary of the recommendations of the guidelines.

Methods An electronic search was conducted on databases, including Pubmed, SinoMed, Wangfang Data, CHKD,VIP, NICE, WHO, GIN and Medliveto retrieve data of the clinical practice guidelines on UTI from the establishment of the database to June 2020. Four assessors assessed the quality of guidelines using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) and evaluated the specific recommendations in guidelines.

Results (1) Nine guidelines including two from the USA (AAP and A guideline for the inpatient care of children with pyelonephritis) and the remaining from EAU/ESPU, SINEPE, KHA-CARI, CPS, ISPN, NICE and CMA-CSP were explored. (2) The AGREE II evaluation demonstrated higher scores of UTI guidelines in terms of 'scope and purpose' (72.99%±11.19%) and 'clarity of presentation' (75.62%±7.75%), whereas the average scores were lower in the aspect of 'stakeholder involvement' (35.49%±14.41%), 'rigour of development' (37.05%±10.05%), 'applicability' (37.75%±11.98%) and 'editorial independence' (43.06%±48.14%). The average scores of the guidelines were as follows: SINePe (72.57%), CMA-CSP (62.96%), EAU/ESPU (59.61%), AAP (56.86%), NICE (47.54%), CPS (40.93%), KHA-CARI (38.86%), ISPN (38.63%) and A guideline for the inpatient care of children with pyelonephritis (34.72%). (3) All the selected guidelines basically reached a consensus on urine sample retention methods in older children, the antibiotic treatment course and renal and bladder ultrasonography application but lacked a conclusion on the determination of urine culture results, the choice of voiding cystourethrography and Tc-99mdimercaptosuccinicacid, and antibiotic prophylaxis.

Conclusion There remains a need to improve the quality of guidelinesfor UTI in clinical practice. Existing controversies on the current guidelines of UTI in some recommendations warrant further exploration to provide more evidence on formulating more unified and practical guidelines in the future.

Ethics and dissemination No ethical approval is required for this research, as it did not include patients or patient data.

Strengths and limitations of this study

► To our knowledge, this is the first study that evaluates the quality of guideline of urinary tract infections (UTIs) in children by Appraisal of Guidelines for Research & Evaluation II (AGREE II).

► Selection bias exists in this study because only guidelines published in English and Chinese were included.

► AGREE II tool does not account for the relative importance of the six domains.

► AGREE II does not provide high-quality and minimum quality rating criteria.

INTRODUCTION

Urinary tract infections (UTIs) are a common clinical infectious disease, especially in infants, with approximately 7% incidence in infants with fever.[1] The lack of specific clinical signs and symptoms largely contributes to missed and misdiagnosis of UTI in infants. Current evidence views UTI in childhood as an indicator of numerous renal diseases. UTI, for instance, has been revealed to be the first symptom in 30% of congenital anomalies of the kidney and urinary tract (CAKUT).[2,3] Recurrent UTIs and CAKUT can certainly cause renal scars, long-term hypertension, some of which potentially progresses to chronic kidney diseases (CKD) and may have a detrimental effect on the quality of life of children. Therefore, it is imperative to practice early diagnosis, standardised treatment and prevention of relapses to reduce renal scar formation and prevent the occurrence of CKD.

The end of the 20th century has seen many countries issuing and/or updating the guidelines of UTIs in children both aimed to guide decision making among clinicians and reduce waste of resources. A consensus was made in 2007 on the diagnosis and management of UTI by the Chinese expert. However, after decades of development, the paediatric branch of the Chinese Medical Association

in 2017 issued evidence-based guidelines of UTIs in children based on the latest research evidence.

In 2009, Appraisal of Guidelines for Research & Evaluation II (AGREE II) was published as a revised version of the original AGREE instrument, and the tool has presently been translated into multiple languages and is receiving wide application to assess the quality of guideline development.[4]

The present study explores the current UTI guidelines in children, evaluates the quality of guideline by AGREE II and compares and contrasts the selected recommendations of the guidelines aiming to provide a scientific basis for clinical diagnosis and treatment.

METHODS
Inclusion and exclusion criteria
Inclusion criteria
1. The literature includes the diagnosis and treatment of UTI.
2. The type of literature is clinical guideline/consensus/norm.
3. The applicable object of the guidelines is limited to children.
4. The latest version of a set of guidelines that has been updated multiple times.
5. A complete guideline text, published in English or Chinese.

Exclusion criteria
Guideline interpretations or translations and traditional Chinese Medicine guidelines were excluded, as well as any documents that were not guidelines (such as reviews and other guideline quality appraisal).

Literature search strategy
The following electronic databases will be searched: PubMed, SinoMed (The Chinese biomedical literature database), China Wanfang Digital Database, VIP database, China Hospital Knowledge Database (CHKD), NICE, WHO, GIN and Medlive, from database inception time to June 2020. The search terms included: urinary tract infection, guideline, practice guidelines as the topic, guidelines, guidance, recommendation, consensus, child, preschool, infant, adolescent, newborn, pediat, youth, toddle, teen, boy, girl and baby. Search strategy is in (online supplemental material 1).

Literature screening and data extraction
Two reviewers (BZ and FD) independently screened the articles according to inclusion and exclusion criteria by reading through the title and abstract. A third reviewer (LY) was consulted in the event of disagreement to reach a consensus. The reviewers used Microsoft office 2019 to extract the basic information from the selected guidelines, including title, guideline developers, country, target population, the

tool of evidence quality and strength, and number of references.

Quality assessment
The research group comprised four clinicians experienced in paediatric nephrology and had been trained by an expert in evidence-based medicine, and they independently evaluated guidelines. The selected guidelines were independently using the AGREE II, which comprised 23 items in six domains: 'Scope and purpose', 'Stakeholder involvement', 'Rigour of development', 'Clarity of presentation', 'Applicability' and 'Editorial independence'. Each item was rated on a seven-point scale from 1 (strongly disagree) to 7 (strongly agree). A scaled domain percentage score was calculated, according to the AGREE II methodology, as follows: $\frac{(obtained\ score - minimum\ possible\ score)}{(maximum\ possible\ score - minimum\ possible)} \times 100\%$. Only the scores in each domain were evaluated because the user manual for AGREE II does not provide high-quality and minimum quality rating criteria.

To resolve discrepancies between the four assessors, a method was used from a previous study: intraclass correlation coefficient (ICC) was calculated to assess inter-rater reliability, ICC values greater than 0.75 demonstrated acceptable stability.[5 6]

Comparison of recommendations
Recommendations on the diagnosis and treatment of UTIs in children reported in the selected guidelines were extracted and presented in comparative tables focusing on possible gaps and common messages.

Data analysis
Descriptive statistics were conducted in order to characterise the recommendation content. For quantitative data and the guidelines basic information, the statistical analysis was performed using Microsoft Office 2019, and ICCs were calculated by SPSS V.22.0.

Ethics and dissemination
No ethical approval is required for this research, as it did not include patients or patient data.

RESULTS
Guideline selection
Of the 37 full texts retrieved and screened, nine articles were included in this study, including the USA[7 8] (two articles), Europe[9] (one article), Italy[10] (one article), Australia[11] (one article), Canada[12] (one article), India[13] (one article), UK[14] (one article) and China[15] (one article). The selected guidelines comprised nine medicine societies (AAP, EAU, ESPU, SINePe, KHA-CARI, CPS, ISPN, NICE, and CMA-CSP). Figure 1 (flow diagram of literature retrieval) shows the guideline screening process. Table 1 shows the basic information of the selected guidelines.
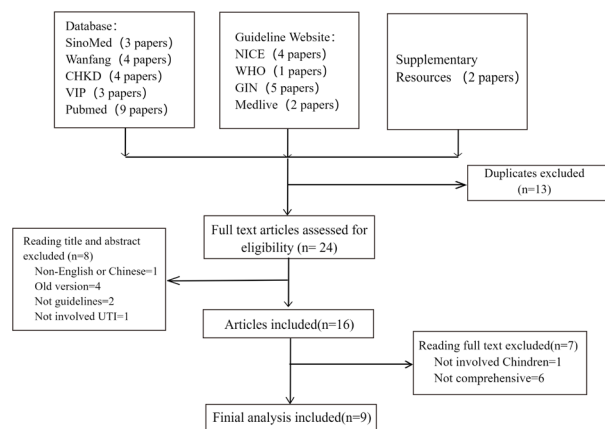
Figure 1. Flow diagram of literature retrieval

Figure 1 Flow diagram of literature retrieval. CHKD, China Hospital Knowledge Database.

Quality assessment

The four assessors independently evaluated the selected guidelines, and the scores are in (online supplemental material 2). Inter-rater reliability of the four assessors total scores was assessed using ICC (table 2). ICC values for all the nine guidelines were greater than 0.75 (0.787~0.925), providing evidence of high consistency in the assessment results between the four assessors. Table 3 illustrate the scores of the AGREE II quality assessment.

Scores of the six domains

1. Scope and purpose: this domain yielded an average score of 72.99%±11.19%. NICE demonstrated the highest score in this domain at 91.76%, while KHA-CARI showed the lowest score at 54.17%.
2. Stakeholder involvement: this domain yielded an average score of 35.49%±14.41%. SINePe demonstrated the highest score in this domain at 91.76%, while the USA guideline for the inpatient care of children with pyelonephritis showed the lowest score at 12.5%.
3. Rigour of development: this domain yielded an average score of 37.05%±10.05%. CMA-CSP demonstrated the highest score in this domain at 54.17%.
4. Clarity of presentation: this domain yielded an average score of 75.62%±7.75%. AAP demonstrated the highest score in this domain at 54.17%.
5. Applicability: this domain yielded an average score of 37.75%±11.98%. CMA-SINePe demonstrated the highest score in this domain at 54.17%.
6. Editorial independence: this domain yielded an average score of 43.06%±48.14%. Four guidelines AAP, EAU/ESPU, SINePe and CMA-CSP, scored more than 90%.

Scores of the nine guidelines

The average score for selected guidelines (from high to low) were as follows: SINePe (72.57%), CMA-CSP (62.96%), EAU/ESPU (59.61%), AAP (56.86%), NICE (47.54%), CPS (40.93%), KHA-CARI (38.86%), ISPN (38.63%) and the guideline for the inpatient care of children with pyelonephritis (34.72%).

Summary of recommendations
Similarities

1. A clean voided midstream urine sample is the preferred method for UTI diagnosis for toilet-trained children.
2. The choice of antibiotic should be based on resistance patterns of urinary pathogens, and the course of treatment of antibiotics is generally 3–4 days for lower urinary tract infection and 7–14 days for upper UTI.
3. Renal and bladder ultrasonography (RBUS) is recommended for all children with febrile UTI (except NICE), but voiding cystourethrography (VCUG) and Tc-99mdimercaptosuccinicacid (DMSA) are not regarded as routine examinations.
4. Antibiotic prophylaxis is not routinely recommended after the first febrile UTI, excepting high-grade VUR.

Differences

1. Urine collection method for non-toilet-trained children: AAP, EAU/ESPU, ISPN and the guideline for pyelonephritis in the USA are more inclined to bladder catheterisation (BC) and suprapubic aspiration (SPA); other guidelines (except CMA-CSP) recommend urinary bag or clean voided urine (CVU).
2. The guidelines (except NICE) recommend that the positive urinalysis be dependent on the urine collection method. Table 4 illustrates the specific results.
3. The recommendations for imaging evaluation slightly differ. Generally, the guidelines of AAP, EAU/ESPU, KHA-CARI, SINePe and CPS do not recommend for the sequence of VCUG and DMSA, while ISPN, NICE, CMA-CSP and the guideline for pyelonephritis in the USA tend to prioritise DMSA examination and give different opinions based on the age of the children. Table 4 illustrates the specific results.
4. There is no consistent regulation on the dose and course of antibiotic prophylaxis (EAU/ESPU, SINePe, KHA-CARI, CPS, ISPN and CMA-CSP), in particular, AAP and NICE failed to address this aspect. Table 4 illustrates the specific results.

DISCUSSION
Quality appraisal of the guidelines for UTIs in children with AGREE II

Nine guidelines have been analysed in this study. The quality appraisal with AGREE II demonstrated that four guidelines (SINePe, CMA-CSP, EAU/ESPU and AAP) exhibited scores greater than 50%. Among the six fields of the AGREE II tool, the scores of domain 1 'scope and purpose' and domain 4 'clarity of presentation' were >70%, while the scores of the other four fields were lower than 50%.

Of note, the rigour of development better reflected the quality of the guidelines. We reported low scores of guidelines in domain 3 (rigour of development), which is consistent with the previous findings by Chen *et al*.[16] In the present study, the Chinese guideline exhibited the highest score in domain 3, particularly because it

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Table 1 The basic information of the selected guidelines

Title	Source	Organisation/author	Country	Year of publication	Target population	The criteria for selecting the evidence	Number of references
Reaffirmation of AAP clinical practice guideline: the diagnosis and management of the initial urinary tract infection in febrile infants and young children 2–24 months	Pediatrics	AAP	USA	2016	Infants and young children 2–24 months	AAP policy	17
Urinary tract infections in children: EAU/ESPU Guidelines	European Urology	EAU/ESPU	Europe	2014	Children	EAU guidelines criteria—modified GRADE	118
Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children	*Acta Paediatrica*	SINePe	Italy	2019	Infants and young children 2–36 months	SOTR	107
KHA-CARI guideline: diagnosis and treatment of urinary tract infection in children	Asian Pacific Society of Nephrology	KHA-CARI	Australia	2014	Children	GRADE	18
Urinary tract infections in infants and children: diagnosis and management	Paediatrics and child health	CPS	Canada	2014	Infants older than 2 months	Not described	33
Revised statement on management of urinary tract infections	Indian paediatrics	ISPN	India	2011	Children	Not described	26
Urinary tract infection in under 16s: diagnosis and management	NICE website	NICE	UK	2018	Children under 16s	Not described	/
A guideline for the inpatient care of children with pyelonephritis	*Annals of Saudi Medicine*	Aftab S Chishti	USA	2010	Hospitalised children	Not described	63
Evidence-based guideline on diagnosis and treatment of urinary tract infection (2016)	*Chinese Journal of Pediatrics*	CMA-CSP	China	2017	Children	ESC guidelines criteria	18

AAP, American Academy of Pediatrics; CMA-CSP, Chinese Medical Association, Chinese Society of Pediatrics; CPS, Canadian Pediatric Society; EAU, European Association of Urology; ESC, European Society of Cardiology; ESPU, European Society for Pediatric Urology; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ISPN, Indian Pediatric Nephrology Group; KHA-CARI, Kidney Health Australia, Caring for Australasians with Renal Impairment; NICE, National Institute for Health and Care Excellence; SINePe, Italian Society of Pediatric Nephrology; SORT, Strength of recommendation taxonomy.

describes the evidence selection criteria and the search methods for the evidence. Moreover, EAU/ESPU, SINePe and KHA-CARI describe the evidence selection criteria and the methods for formulating the recommendations. There is a previous suggestion that guidelines be updated every 3–5 years.[17] The publishing period in the present study is between 2010 and 2019, and five guidelines (ISPN, CPS, KHA-CARI, EAU/ESPU and the guideline for the inpatient care of children with pyelonephritis) had not been updated for more than 5 years.

SINePe demonstrated the highest applicability score because it considered the obstacles in the application of recommendations. For example, this guideline does not recommend a new imaging technique—contrast-enhanced voiding urosonography (ceVUS)—because it is time consuming, expensive and not available on a large

Table 2 Intraclass correlation coefficient (ICC)

Guideline	ICC	95% CI	P value
AAP	0.925	0.865 to 0.964	< 0.001
EAU/ESPU	0.908	0.836 to 0.955	< 0.001
SINePe	0.913	0.845 to 0.958	< 0.001
KHA-CARI	0.894	0.814 to 0.948	< 0.001
CPS	0.890	0.807 to 0.946	< 0.001
ISPN	0.799	0.666 to 0.898	< 0.001
NICE	0.850	0.742 to 0.925	< 0.001
Pyelonephritis guideline	0.905	0.831 to 0.954	< 0.001
CMA-CSP	0.895	0.814 to 0.948	< 0.001

scale, despite its high specificity, sensitivity and safety in VUR diagnosis. Other guidelines demonstrated low scores in domain 5 because they omit facilitators, barriers and potential resource implications of its application. These data strongly recommend the need to develop new guidelines, involving health economists, who can fully consider the cost-effectiveness of recommendations, to improve the applicability of the guidelines.

The development of many guidelines is funded by bodies, such as governments, professional associations and pharmaceutical companies. There should be an explicit statement that these bodies have not influenced the recommendations. In the present study, AAP, EAU/ESPU, SINePe and CMA-CSP guidelines provided statements regarding the source of funding and competing interests. Other guidelines did not provide such statements. In future, its importance for guideline developers to clarify their editorial independence to improve credibility of guidelines.

Comparison of recommendations in the selected guidelines

The selected guidelines reached a consensus in urine collection methods for toilet-trained children, RBUS application and treatment courses. However, there is

no consensus on the standard of positive urine culture results, the choice of VUCG and DMSA and antibiotic prophylaxis.

Moreover, the criteria for determining the positive or negative results of urine culture varied across urine collection methods. Previously in 2016, a study reported 80% bacterial counts in children with UTI greater than $50\,000\,CFU/mL$[18]; notably, AAP adopted this criterion. However, because low colony counts can be indicative of a UTI in some circumstances, EAU/ESPU outlines $1000–50000\,CFU/mL$ as the criteria of BC. Swerkersson *et al*'s study reported similar results whereby 19% bacterial counts lower than $10^4\,CFU/mL$ were found in the first diagnosis of UTI infants by SPA,[19] which is in agreement with CPS.

Regarding the choice for imaging, no uniform opinions have been relayed on the order of VCUG and DMSA. Currently, two approaches, the 'top-down' method (DMSA scan and, if positive, VCUG) and the 'down-top' method (VCUG and, if positive, DMSA scan), have been described. Our analysis revealed that NICE, CMA-CSP, ISPN and the guideline for pyelonephritis in the USA tend to emulate the 'top-down' method, which can allow for early kidney damage assessment. Previous evidence indicates that UTI and renal scarring can occur in patients without VUR, and many renal scars are associated with the fetal period, therefore, may present renal dysplasia.[20] In addition, DMSA demonstrates an upstanding predictive ability for high-grade VUR (99% sensitivity), which is why the 'top-down' method not only can decrease patient discomfort caused by invasive examinations but also save medical costs.[21] Contrarily, the VUR-based 'down-top' method is strongly associated with renal scar formation and UTI recurrence. As such, early diagnosis and treatment of VUR are imperative in preventing further kidney damage. It is of particular note that the guideline of the American College of Radiology in 2017 recommends this method but does not recommend DMSA regardless of children's age.[22] Overall, in clinical practice, whether

Table 3 Standardised scores of each domain by AGREE II of guidelines

	Scope and purpose (%)	Stakeholder involvement (%)	Rigour of development (%)	Clarity of presentation (%)	Applicability (%)	Editorial independence (%)	Average scores (%)
AAP	69.44	26.39	36.98	87.50	25.00	95.83	56.86
EAU/ESPU	75.00	31.94	45.83	73.61	33.33	97.92	59.61
SINePe	88.89	55.56	48.96	84.72	61.46	95.83	72.57
KHA-CARI	54.17	25.00	34.90	84.72	34.38	0.00	38.86
CPS	73.61	26.39	39.58	70.83	35.42	0.00	40.97
ISPN	62.50	40.28	25.52	63.89	39.58	0.00	38.63
NICE	91.67	41.67	26.56	72.22	53.13	0.00	47.54
Pyelonephritis guideline	66.67	12.50	25.00	75.00	29.17	0.00	34.72
CMA-CSP	75.00	59.72	54.17	68.06	22.92	97.92	62.96
Means±SD (%)	72.99±11.19	35.49±14.41	37.50±10.05	75.62±7.75	37.15±11.98	43.06±48.14	/

Table 4 Summary of recommendations

	Criteria positive of urine culture	Antibiotic prophylaxis	Imaging			
			Age	**RBUS**	**VCUG**	**DMSA**
AAP	BC/SPA: ≥5×10^4 CFU/mL	/	2–24 months	All of febrile infants	Abnormal RBUS or other specific circumstances	/
EAU/ESPU	SPA: any; BC: ≥10^3–5×10^4 CFU/mL; CVU: ≥10^4 CFU/mL with symptoms or ≥10^5 CFU/mL without symptoms	VUR III–V	/	All of febrile children	In febrile UTI children: <1 year, >1 year girl, >1 year boy with recurrent febrile UTI and toilet-trained children who were suspected of VUR	
SINePe	SPA: >10^4 CFU/mL BC: >10^4 CFU/mL CVU: >5×10^4 CFU/mL Urinary bag: >10^5 CFU/mL	VUR IV–V, recurrent febrile UTI; dose: one-quarter to one-third of the treatment dose; course: 12–24 months in girls and 6–12 months in boys.	2–36 months	All of febrile children*	Abnormal RBUS or other high-risk factors†	VUR IV–V
KHA-CARI	SPA: any; BC: >10^5 CFU/mL; CVU: >10^5 CFU/mL	A severe index UTI, recurrent UTI, VUR III–V; course: 6–24 months low dose	/	First UTI, not had antenatal ultrasound, had some special cases‡	Abnormal RBUS; recurrent pyelonephritis	Renal functional decline
CPS	CVU: ≥5×10^5 CFU/mL BC: ≥5×10^4 CFU/mL SPA: any	VUR IV-V	<2 years	All of febrile infants	Abnormal RBUS; recurrent UTI in children <2 years	Only when the diagnosis of UTI is in doubt
			>2 years	/		
ISPN§	SPA: any; BC: >5×10^4 CFU/mL CVU: >10^5 CFU/mL	All grades of VUR, recurrent UTI; Low dose; Course: VUR I-II until 1y old, VUR III-V up to 5y;	<1 years	All UTI children	First UTI in children	First UTI in children
			1–5 years		Abnormal RBUS or DMSA	First UTI in children
			>5 years		Abnormal RBUS	Abnormal RBUS
NICE	/	/	<6 months	All children¶	Atypical/recurrent UTI	Atypical/recurrent UTI
			6 months–3 years	Atypical/recurrent UTI	Not recommend	Atypical/recurrent UTI
			>3 years	Atypical/recurrent UTI	Not recommend	Recurrent UTI
Pyelonephritis guideline**	CVU: >10^4 CFU/mL in boys and >10^5 CFU/mL in girls; BC: >10^4 CFU/mL	Not recommend	All	Boys	Abnormal DMSA	Boys
			< 3 years	Girls		Girls
			3–7 years	Girls with fever >38.5℃		Girls with fever >38.5℃
			> 7 years	Girls do not take any imaging examination		
CMA-CSP††	SPA: any G⁻bacteria, G⁺bacteria >10^3 CFU/mL; BC: >10^5 CFU/mL; CVU: >10^4 CFU/mL in boys, and three times >10^5 CFU/mL in girls	Dilated VUR, recurrent UTI; dose: one-third of treatment dose	≤2 years	First febrile UTI	Abnormal RBUS or DMSA; atypical UTI; recurrent UTI	First febrile UTI
			> 2 years		When RBUS is abnormal, performed as a programme of ≤2 years	

*Not recommend RBUS during the febrile UTI, unless it is complicated, atypical or severe (presence of any of the following: septic state, fever persisting after 3 days of appropriate antibiotic treatment, elevated plasma creatinine, oliguria).
†First-degree relative with VUR, septicaemia, chronic kidney disease, age <6 months in a male infant, likely non-compliance of the family, abnormal bladder emptying, no clinical response to correct antibiotic treatment within 72 hours, bacteria other than *Escherichia coli*.
‡Special cases: bacteraemia,<3 months of age, atypical organisms (eg, *Staphylococcus aureus* or Pseudomonas), no clinical response to correct antibiotic treatment within 48 hours, renal impairment or significant electrolyte derangement, abdominal mass, poor urinary stream.
§Imaging evaluation of the first UTI.
¶For infants younger than 6 months with a first-time UTI that responds to treatment, ultrasound should be carried out within 6 weeks of the UTI.
**Imaging evaluation of the first pyelonephritis.
††Imaging evaluation of the first febrile UTI.
BC, bladder catheterisation; CVU, clean voided urine; RBUS, renal and bladder ultrasonography; SPA, suprapubic aspiration; UTI, urinary tract infection.

to apply the 'top-down' or 'down-top' approach should decide based on actual situation of patients.

SINePe guideline outlined a new imaging technique—ceVUS—that shows the ureter and bladder in real-time using ultrasound contrast agents. Compared with VCUG, it has the advantages of real-time imaging, radiation free and favourable safety profile. Mounting evidence shows that ceVUS is highly sensitive

(80%–100%) and accurate (77%–86%) in the diagnosis of VUR, and the diagnosis agreement between VCUG and ceVUS is greater than 70%.[23–27] EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guideline and Chinese expert consensus about VUR recommend the application of ceVUS in the following situations: (1) first examination for VUR in girls; (2) follow-up examinations for VUR in girls and boys after conservative or surgical therapy; and (3) screening high-risk patients for reflux.[28 29] In this view, ceVUS holds promise as a preferred choice for VUR screening in the future.

For antibiotic prophylaxis, most selected guidelines (except NICE and AAP) recommend its application for high-grade VUR, but no consensus has been made on the regulation of the dose and course. SINePe suggests one-quarter to one-third of the treatment dose and duration of prophylaxis is 12-24 months in girls and 6-12 months in boys; however, ISPN has a different view that antibiotic prophylaxis can be until 1 year old for VUR I–II and 5 years old for VUR III–IV. Meanwhile, we cannot ignore some dissents of benefit and risk assessment of antibiotic prophylaxis. Some researchers revealed that long-term antibiotic prophylaxis plays no or insignificant role in preventing UTI recurrence but increases the risk of resistant strains significantly.[30 31] These data suggest the need to discuss and tailor the decision to use antibiotic prophylaxis in an individualised fashion.

Study limitations

First, selection bias exists in this study because only guidelines published in English and Chinese were included. Second, we may have missed some guidelines because of the limitation of the search strategy. Third, AGREE II tool has some limitations, for example, it does not account for the relative importance of the six domains, domain 3 (rigour of development) is considered of equal importance to other domains. There is a need to carefully consider the recommendations if the scores for domain 3 are low.

In conclusion, although the current guidelines of UTI in children can be adopted in clinical practice, their qualities are uneven. As such, there is a whole lot of room for improvement, especially in the areas of the rigour of development, applicability, editorial independence and stakeholder involvement. Additionally, the existing controversial opinions warrants continued exploration to provide powerful evidence.

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Database：PubMed

Year limit：from database-inception time to June 2020

Search Strategy：

#1   "Urinary Tract Infection"[Mesh]

#2   Urinary Tract Infection[Title/Abstract]

#3   Infection, Urinary Tract[Title/Abstract]

#4   Infections, Urinary Tract[Title/Abstract]

#5   Tract Infection, Urinary[Title/Abstract]

#6   Tract Infections, Urinary[Title/Abstract]

#7   #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8   "Guideline" [Publication Type]

#9   "Practice Guidelines as Topic"[Mesh]

#10 Guidelines[title]

#11 Guideline[title]

#12 Guidance[title]

#13 Recommendation[title]

#14 consensus[title]

#15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

#16 "Child"[Mesh]

#17 "Child, Preschool"[Mesh]

#18 "Infant"[Mesh]

#19 "Adolescent"[Mesh]

#20 "Infant, Newborn"[Mesh]

#21 (child[Title/Abstract] OR pediat[Title/Abstract] OR paediat[Title/Abstract] OR infan[Title/Abstract] OR youth[Title/Abstract] OR toddle[Title/Abstract] OR adolesc[Title/Abstract] OR teen[Title/Abstract] OR boy[Title/Abstract] OR girl[Title/Abstract] OR bab[Title/Abstract] OR preschool[Title/Abstract] OR pre-school[Title/Abstract])

#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23 #7 AND #15 AND #22

Database：SinoMed

Year limit：from database-inception time to June 2020

Search Strategy：

#1   "泌尿道感染"[不加权:扩展]

#2   "泌尿道感染"[常用字段:智能]

#3   "泌尿系感染"[常用字段:智能]

#4   "尿路感染"[常用字段:智能]

#5   "尿道感染"[常用字段:智能]

#6   #1 OR #2 OR #3 OR #4 OR #5

#7   "指南"[不加权:扩展]

#8   "指南"[常用字段:智能]

#9   "指引"[常用字段:智能]

#10 "共识"[常用字段:智能]

#11 "规范"[常用字段:智能]

#12 "草案"[常用字段:智能]

#13 #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 "儿童"[不加权:扩展]

#15 "婴儿"[不加权:扩展]

#16 "青少年"[不加权:扩展]

#17 "未成年人"[不加权:扩展]

#18 儿童 OR 婴儿 OR 小儿 OR 新生儿 OR 早产儿 OR 未成年 OR 学龄前 OR 幼儿 OR 青少年

#19 少年 OR 患儿 OR 儿科 OR 少女 OR 少男 OR 少儿 OR 青春期 OR 病儿 OR 学生

#20 #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 #6 AND #13 AND #20

Database：CHKD

Year limit：from database-inception time to June 2020

Search Strategy：

#1 "泌尿道感染"[主要主题]

#2 "泌尿道感染"[题名/关键词/摘要]

#3 "泌尿系感染"[题名/关键词/摘要]

#4 "尿路感染"[题名/关键词/摘要]

#5 "尿道感染"[题名/关键词/摘要]

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 "指南"[主要主题]

#8 "指南"[题名/关键词/摘要]

#9 "指引"[题名/关键词/摘要]

#10 "共识"[题名/关键词/摘要]

#11 "规范"[题名/关键词/摘要]

#12 "草案"[题名/关键词/摘要]

#13 #6 AND (#7 OR #8 OR #9 OR #10 OR #11 OR #12)

#14 "儿童"[主要主题]

#15 "儿童"[题名/关键词/摘要]

#16 "小儿"[题名/关键词/摘要]

#17 "幼儿"[题名/关键词/摘要]

#18 "婴幼儿"[题名/关键词/摘要]

#19 "新生儿"[题名/关键词/摘要]

#20 #13 AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19)

Database：Wangfang Data

Year limit：from database-inception time to June 2020

Search Strategy：

#1 "泌尿道感染"[主题] OR "泌尿道感染"[题名或关键词] OR "泌尿系感染"[题名或关键词]OR "尿路感染"[题名或关键词] OR "尿道感染"[题名或关键词]

#2 "指南"[主题] OR "指南"[题名或关键词] OR "指引"[题名或关键词] OR "共识"[题名或关键词] OR "规范"[题名或关键词] OR "草案"[题名或关键词]

#3 "儿童"[主题] OR "儿童"[题名或关键词] OR "小儿"[题名或关键词] OR "幼儿"[题名或关键词] OR "婴幼儿"[题名或关键词] OR "新生儿"[题名或关键词]

#4 #1 AND #2 AND #3

Database：VIP

Year limit：from database-inception time to June 2020

Search Strategy：

#1 "泌尿道感染"[题名或关键词] OR "泌尿系感染"[题名或关键词]OR "尿路感染"[题名或关键词] OR "尿道感染"[题名或关键词]

#2 "指南"[题名或关键词] OR "指引"[题名或关键词] OR "共识"[题名或关键词] OR "规范"[题名或关键词] OR "草案"[题名或关键词]

#3 "儿童"[题名或关键词] OR "小儿"[题名或关键词] OR "幼儿"[题名或关键词] OR "婴幼儿"[题名或关键词] OR "新生儿"[题名或关键词]

#4 #1 AND #2 AND #3

Website：NICE (https://www.nice.org.uk/guidance/published?type=cg)

Search Data：06-23-2020

Search Term：Urinary Tract Infection

Website：GIN (https://www.g-i-n.net)

Search Data：06-23-2020

Search Term：Urinary Tract Infection

Website：WHO (http://apps.who.int/iris/?locale=zh)

Search Data：06-23-2020

Search Terms：Urinary Tract Infection, Guideline, Child

Website：Medlive (http://guide.medlive.cn/)

Search Data：06-23-2020

Search Terms：泌尿系感染；泌尿道感染；尿路感染；尿道感染；肾盂肾炎；膀胱炎

AAP	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1			Domain scores	69.44%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	6	4	4	4	18
Item 2	4	4	6	4	18
Item 3	6	7	6	7	26
Total	16	15	16	15	**62**

Domain 2			Domain scores	26.39%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	4	7	5	7	23
Item 5	1	1	1	1	4
Item 6	1	1	1	1	4
Total	6	9	7	9	**31**

Domain 3			Domain scores	36.98%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	2	1	2	6
Item 8	1	1	1	1	4
Item 9	4	6	5	6	21
Item 10	1	1	1	1	4
Item 11	6	6	3	6	21
Item 12	6	7	7	7	27
Item 13	1	1	1	1	4
Item 14	5	4	3	4	16
Total	25	28	22	28	**103**

Domain 4			Domain scores	87.50%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Tota
Item 15	7	6	6	6	25
Item 16	5	7	6	6	24
Item 17	7	7	6	6	26
Total	19	20	18	18	**75**

Domain 5			Domain scores	25.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	1	1	4
Item 19	1	1	1	1	4
Item 20	2	3	2	3	10
Item 21	5	6	5	6	22
Total	9	11	9	11	**40**

Domain 6			Domain scores	97.92%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	7	7	6	7	27
Item 23	7	7	6	7	27
Total	14	14	12	14	**54**

EAU/ESPU	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	
Domain 1			Domain scores	75.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	6	7	7	7	27
Item 2	5	6	6	4	21
Item 3	3	6	4	5	18
Total	14	19	17	16	**66**
Domain 2			Domain scores	31.94%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	6	7	7	7	27
Item 5	1	1	1	1	4
Item 6	1	1	1	1	4
Total	8	9	9	9	**35**
Domain 3			Domain scores	**45.83%**	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	5	5	6	4	20
Item 8	2	3	3	4	12
Item 9	2	4	1	4	11
Item 10	5	6	6	6	23
Item 11	6	6	5	6	23
Item 12	5	6	6	6	23
Item 13	1	1	1	1	4
Item 14	1	1	1	1	4
Total	27	32	29	32	**120**
Domain 4			Domain scores	73.61%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	6	5	6	5	22
Item 16	4	6	5	6	21
Item 17	4	6	6	6	22
Total	14	17	17	17	**65**
Domain 5			Domain scores	33.33%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	1	1	4
Item 19	5	4	3	4	16
Item 20	1	1	1	1	4
Item 21	6	7	4	7	24
Total	13	13	9	13	**48**
Domain 6			Domain scores	97.92%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	7	7	6	7	27
Item 23	7	7	7	7	28
Total	14	14	13	14	**55**

SINePe	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	
Domain 1			Domain scores	88.89%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	6	7	6	7	26
Item 2	4	7	6	5	22
Item 3	7	7	7	7	28
Total	17	21	19	19	**76**
Domain 2			Domain scores	55.56%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	5	7	4	6	22
Item 5	1	1	1	1	4
Item 6	7	6	7	6	26
Total	13	14	12	13	**52**
Domain 3			Domain scores	48.96%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	2	2	2	7
Item 8	4	5	6	5	20
Item 9	5	6	5	6	22
Item 10	4	6	4	6	20
Item 11	5	7	6	7	25
Item 12	5	6	5	6	22
Item 13	1	2	1	2	6
Item 14	1	1	1	1	4
Total	26	35	30	35	**126**
Domain 4			Domain scores	84.72%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	6	6	6	6	24
Item 16	6	6	6	6	24
Item 17	5	7	6	7	25
Total	17	19	18	19	**73**
Domain 5			Domain scores	61.46%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	4	4	4	4	16
Item 19	5	4	5	5	19
Item 20	3	4	3	4	14
Item 21	6	7	6	7	26
Total	18	19	18	20	**75**
Domain 6			Domain scores	95.83%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	7	7	6	7	27
Item 23	7	7	6	7	27
Total	14	14	12	14	**54**

KHA-CARI	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1			Domain scores	54.17%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	3	4	5	2	14
Item 2	3	6	5	4	18
Item 3	3	6	4	6	19
Total	9	16	14	12	**51**

Domain 2			Domain scores	25.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	4	6	4	6	20
Item 5	1	1	1	1	4
Item 6	1	1	3	1	6
Total	6	8	8	8	**30**

Domain 3			Domain scores	34.90%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	1	1	1	4
Item 8	1	1	1	1	4
Item 9	5	7	6	7	25
Item 10	6	4	4	5	19
Item 11	5	4	5	4	18
Item 12	4	6	5	6	21
Item 13	1	1	1	1	4
Item 14	1	1	1	1	4
Total	24	25	24	26	**99**

Domain 4			Domain scores	84.72%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	6	6	6	6	24
Item 16	5	6	6	6	23
Item 17	6	7	6	7	26
Total	17	19	18	19	**73**

Domain 5			Domain scores	34.38%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	1	1	4
Item 19	6	4	5	4	19
Item 20	1	1	1	1	4
Item 21	5	6	5	6	22
Total	13	12	12	12	**49**

Domain 6			Domain scores	0.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	1	1	1	1	4
Item 23	1	1	1	1	4
Total	2	2	2	2	**8**

CPS	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1			Domain scores	73.61%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	5	7	5	4	21
Item 2	5	4	5	4	18
Item 3	5	7	7	7	26
Total	15	18	17	15	**65**

Domain 2			Domain scores	26.39%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	6	6	4	6	22
Item 5	1	1	1	1	4
Item 6	1	1	2	1	5
Total	8	8	7	8	**31**

Domain 3			Domain scores	39.58%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	1	1	1	4
Item 8	1	1	1	1	4
Item 9	4	3	7	3	17
Item 10	2	3	3	3	11
Item 11	6	6	5	6	23
Item 12	6	6	5	6	23
Item 13	4	4	4	4	16
Item 14	2	3	2	3	10
Total	26	27	28	27	**108**

Domain 4			Domain scores	70.83%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	6	5	6	5	22
Item 16	5	4	6	4	19
Item 17	6	5	6	5	22
Total	17	14	18	14	**63**

Domain 5			Domain scores	35.42%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	1	1	4
Item 19	6	4	5	4	19
Item 20	1	1	1	1	4
Item 21	6	6	5	6	23
Total	14	12	12	12	**50**

Domain 6			Domain scores	0.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	1	1	1	1	4
Item 23	1	1	1	1	4
Total	2	2	2	2	**8**

ISPN	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	
Domain 1			Domain scores	62.50%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	5	7	6	6	24
Item 2	5	7	6	4	22
Item 3	3	2	2	4	11
Total	13	16	14	14	**57**
Domain 2			Domain scores	40.28%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	5	7	3	7	22
Item 5	1	1	2	1	5
Item 6	3	4	4	3	14
Total	9	12	9	11	**41**
Domain 3			Domain scores	25.52%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	2	1	1	1	5
Item 8	1	1	1	1	4
Item 9	1	3	1	3	8
Item 10	6	7	5	7	25
Item 11	4	3	4	3	14
Item 12	4	4	4	4	16
Item 13	1	1	2	1	5
Item 14	1	1	1	1	4
Total	20	21	19	21	**81**
Domain 4			Domain scores	63.89%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	5	4	6	4	19
Item 16	5	5	6	5	21
Item 17	5	4	5	4	18
Total	15	13	17	13	**58**
Domain 5			Domain scores	39.58%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	2	3	3	3	11
Item 19	6	4	5	5	20
Item 20	1	1	1	1	4
Item 21	6	6	1	6	19
Total	15	14	10	15	**54**
Domain 6			Domain scores	0.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	1	1	1	1	4
Item 23	1	1	1	1	4
Total	2	2	2	2	**8**

NICE	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1				Domain scores	91.67%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	7	7	6	7	27
Item 2	7	6	6	6	25
Item 3	7	7	5	7	26
Total	21	20	17	20	**78**

Domain 2				Domain scores	41.67%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	1	2	1	2	6
Item 5	1	4	3	4	12
Item 6	7	7	3	7	24
Total	9	13	7	13	**42**

Domain 3				Domain scores	26.56%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	1	1	1	4
Item 8	1	1	1	1	4
Item 9	3	3	1	3	10
Item 10	2	1	2	1	6
Item 11	4	5	4	5	18
Item 12	5	4	6	4	19
Item 13	1	1	1	1	4
Item 14	4	4	6	4	18
Total	21	20	22	20	**83**

Domain 4				Domain scores	72.22%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	7	5	6	5	23
Item 16	4	4	6	4	18
Item 17	7	5	6	5	23
Total	18	14	18	14	**64**

Domain 5				Domain scores	53.13%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	3	1	6
Item 19	7	6	6	6	25
Item 20	3	5	3	5	16
Item 21	6	5	4	5	20
Total	17	17	16	17	**67**

Domain 6				Domain scores	0.00%
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	1	1	1	1	4
Item 23	1	1	1	1	4
Total	2	2	2	2	**8**

Pyelonephritis guideline	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1			Domain scores	66.67%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	6	7	6	5	24
Item 2	6	6	4	4	20
Item 3	5	5	2	4	16
Total	17	18	12	13	**60**

Domain 2			Domain scores	12.50%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	2	3	3	4	12
Item 5	1	1	1	1	4
Item 6	1	1	2	1	5
Total	4	5	6	6	**21**

Domain 3			Domain scores	25.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	1	1	1	1	4
Item 8	1	1	3	1	6
Item 9	4	3	3	5	15
Item 10	1	1	1	1	4
Item 11	4	6	5	6	21
Item 12	5	6	5	6	22
Item 13	1	1	1	1	4
Item 14	1	1	1	1	4
Total	18	20	20	22	**80**

Domain 4			Domain scores	75.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	6	6	5	6	23
Item 16	5	6	5	6	22
Item 17	4	5	6	6	21
Total	15	17	16	18	**66**

Domain 5			Domain scores	29.17%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	1	1	1	1	4
Item 19	4	3	3	3	13
Item 20	1	1	1	1	4
Item 21	6	6	5	6	23
Total	12	11	10	11	**44**

Domain 6			Domain scores	0.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	1	1	1	1	4
Item 23	1	1	1	1	4
Total	2	2	2	2	**8**

Supplemental material

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CMA-CSP	Assessor 1 Zhu BH	Assessor 2 Liang Y	Assessor 3 Mi L	Assessor 4 Duan F	

Domain 1			Domain scores	75.00%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 1	6	7	5	7	25
Item 2	5	5	5	5	20
Item 3	6	6	3	6	21
Total	17	18	13	18	**66**

Domain 2			Domain scores	59.72%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 4	6	6	5	6	23
Item 5	1	1	1	1	4
Item 6	7	7	7	7	28
Total	14	14	13	14	**55**

Domain 3			Domain scores	54.17%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 7	6	6	6	6	24
Item 8	7	6	6	6	25
Item 9	5	6	6	6	23
Item 10	2	5	3	5	15
Item 11	5	4	5	4	18
Item 12	5	5	6	5	21
Item 13	1	1	3	1	6
Item 14	1	1	1	1	4
Total	32	34	36	34	**136**

Domain 4			Domain scores	68.06%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 15	5	6	6	6	23
Item 16	6	4	6	4	20
Item 17	5	4	5	4	18
Total	16	14	17	14	**61**

Domain 5			Domain scores	22.92%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 18	2	1	1	1	5
Item 19	1	1	3	1	6
Item 20	1	1	1	1	4
Item 21	6	6	5	6	23
Total	10	9	10	9	**38**

Domain 6			Domain scores	97.92%	
	Assessor 1	Assessor 2	Assessor 3	Assessor 4	Total
Item 22	7	7	6	7	27
Item 23	7	7	7	7	28
Total	14	14	13	14	**55**