DJ Brinkman*
GW Disselhorst*
BHE Jansen
J Tichelaar
MA van Agtmael
TP de Vries
MC Richir

* The first two authors contributed equally to this work

4.1

What should junior doctors know about the drugs they frequently prescribe? A Delphi study among physicians in the Netherlands

Basic & Clinical Pharmacology & Toxicology 2016;118(6):456-461

ABSTRACT

Aim

The aim of this study was to assess the factual knowledge of commonly prescribed drugs that junior doctors should know by heart in order to prescribe rationally in daily practice, defined as Essential Drug Knowledge (EDK).

Methods

A two-round Internet delphi study was carried out involving general practitioners, and registrars and consultants from 2 Dutch academic and 4 teaching hospitals. A preliminary list of 377 potential EDK items of three commonly prescribed drugs was assessed on a dichotomous scale; an item was considered EDK if at least 80% consensus was reached. The consensus list of EDK items was discussed in the research team to identify similarities between the studied drugs, eventually constructing a list of general EDK items that can be extrapolated to other commonly prescribed drugs.

Results

In total, 60 experts considered 93 of the 377 items (25%) as EDK. Based on these findings, the research team constructed a list of 10 general EDK items.

Conclusions

This EDK list can be useful for curriculum development, training programmes and assessment of future junior doctors who must regularly make prescribing decisions.

INTRODUCTION

Rational prescribing (i.e., effectively, safely, and at low cost) is an essential skill for medical doctors to reduce the frequency of avoidable adverse drugs reactions and prescribing errors.[1,2] Unfortunately, numerous studies have revealed that the prescribing performance of junior doctors is inadequate and that they make many avoidable prescribing errors, resulting in inefficiencies in patient care and even patient harm.[1-5] There is considerable evidence that a major factor contributing to prescribing errors is a lack of basic knowledge of pharmacology and pharmacotherapy among recent graduates.[6-16] Thus improving the pharmacology and pharmacotherapy knowledge of medical students might prevent or reduce the number of these errors in the future.[1,6]

In order to prescribe adequately, it is important to identify which information about individual drugs should be ready knowledge and which can be looked up (e.g., by using a mobile app or electronic prescribing system). Some studies suggest that medical students should use, and have a thorough knowledge of, a core list of commonly prescribed drugs, such as the Essential Drug List[17] or the Student Formulary,[18-21] so that they can prescribe these drugs appropriately, under the supervision of a senior doctor. This knowledge of drug information and prescribing competence should be tested in an examination before graduation. Until now, there has been no clear and robust definition of what graduates should know about commonly prescribed drugs (e.g., doses, contraindications etc) in order to prescribe rationally. Therefore, the aim of this study was to identify which information about commonly prescribed drugs junior doctors should have acquired in order to prescribe rationally in daily practice, defined as Essential Drug Knowledge (EDK).

METHODS

Study design

The study was conducted from June 2012 to July 2013. We used a two-round Internet Delphi method to reach consensus on EDK. The Delphi technique is a widely accepted method for identifying desired features of professionals by eliciting expert opinions in successive rounds.[22-24] An advantage of the Delphi process is that face-to-face meetings are not required, so that there is no risk of peer pressure, and experts from different regions can easily participate in the study.[25] The Delphi technique used in our study comprised the following: experts were interviewed by means of electronic questionnaires, answers were collected and aggregated (Round 1), and then refined by the same experts during a second round (Round 2).

Questionnaire development

To identify EDK, we selected three drugs from different classes: amoxicillin (antibiotic), hydrochlorothiazide (diuretic), and diclofenac (non-steroidal anti-inflammatory drug). Junior doctors in the Netherlands would be expected to know about these drugs because they are among the ten most commonly prescribed drugs in the Netherlands,[26] and two (amoxicillin and hydrochlorothiazide) are included in the World Health Organization (WHO) List of essential medicines.[27] For each drug, an initial questionnaire was developed consisting of potential EDK

items. Seventy-seven items for amoxicillin, 100 items for hydrochlorothiazide and 200 items for diclofenac were extracted from the Dutch National Formulary,[28] making a total list of 377 items. All items were divided into six categories of core knowledge:[19] drug class (27 items), pharmacological mechanism of action (42 items), interactions (42 items), contraindications (74 items), side effects (141 items), and methods of administration (51 items). The research team responsible for content development consisted of two pharmacotherapy teachers, one general practitioner (GP), one clinical pharmacologist, and one internist. A sample initial questionnaire section is shown in Figure 1.

Selection of participants

About 40 GPs from one practice cluster, and about 60 consultants and registrars from two Dutch academic and eight teaching hospitals were invited to form an expert panel, to review the relevance of the EDK items. The consultants and registrars came from different disciplines, namely, internal medicine for amoxicillin, cardiology for hydrochlorothiazide, and orthopaedic surgery for diclofenac. As eligibility criteria, all participants had to currently work in clinical practice, supervise medical students or junior doctors, and have at least 3 years of clinical experience.

Category: Pharmacological mechanism of action	Yes	No
Amoxicillin is		
1. a broad-spectrum penicillin	☐	☐
2. a bacteriolytic antibiotic	☐	☐
3. susceptible to degradation by β-lactamase	☐	☐
...		
Category: Contraindications	**Yes**	**No**
A contraindication for amoxicillin is		
1. hypersensitivity to penicillin	☐	☐
2. lymphatic leukaemia	☐	☐
3. infectious mononucleosis	☐	☐
...		

Figure 1. Sample section from Round 1 questionnaire: amoxicillin. For each item listed below, please indicate whether it should be considered essential drug knowledge for junior doctors ('yes' or 'no').

Participants received an e-mail containing instructions about the study's general objective and a web link to the online questionnaire. Participation was anonymous and voluntary; confidentiality was guaranteed.

Questionnaire rounds

Two Delphi rounds were completed for each drug. In the first round, participants were asked to indicate which items, based on their own clinical experience, they considered EDK. For each item, cut-off for progression into the second round was set at 50% consensus for that item; items scoring ≥80% consensus were directly accepted and not reviewed in Round 2. Participants were also asked to add new items if they felt these were missing. In the second round, participants were presented with the items from Round 1 plus the additional suggested items, with each item being shown with the consensus score awarded in the first round. Respondents were allowed to alter their opinion of each item's perceived importance. Only the respondents who took part in the first round were invited back for the second round. All items for which at least 80% consensus was reached were accepted as EDK. The use of a ≥80% consensus cut-off is in line with a previous Delphi study of essential therapeutic information.[29] Round 2 started 1 week after Round 1 was completed. In both rounds, the respondents had 3 weeks to complete the questionnaire. After Round 2, the returned questionnaires were collected in Excel and analysed in IBM SPSS version 20.0 (IBM).

Essential drug knowledge

The final list of EDK items for the three drugs was evaluated by the research team. Within each category, the team identified similarities between the items for the three drugs. Comparison of the items revealed, for example, that common side effects as well as severe or potentially lethal side effects had to be known for all drugs. The research team reached consensus on the most important similarities, with a view to developing a list of general EDK items that can be extrapolated to other commonly prescribed drugs.

RESULTS

Demographic characteristics

In total, 60 experts (20%) completed both questionnaire rounds: 17 for amoxicillin, 20 for hydrochlorothiazide, and 23 for diclofenac. Most of these experts were male (40; 67%), GPs (32; 53%), and they had a median clinical experience of 17 years (range 3–40). Of the consultants and registrars, 22 were working in an academic hospital (79%) and 6 in a teaching hospital (21%).

Essential drug knowledge

During the first round, 228 of the 377 items (60%) were rejected, 81 (22%) were resubmitted in the second round, 6 new items were added (only for amoxicillin), and 68 (18%) were accepted directly (≥80% agreement). During the second round, 62 of the 87 items (71%) were rejected and 25 (29%) were accepted, giving a total of 93 items (25%) considered as EDK. Overall, items in the categories 'drug class' (52%; 14/27) and 'contraindications' (45%; 33/74) were the most accepted;

and items concerning 'side effects' (9%; 9/141) and 'interactions' (14%; 6/42) the fewest (Figure 2). The final list of EDK per drug can be found in Appendix 1, together with the agreement among panel participants, and whether consensus was achieved in the first or second round. On the basis of this list, the research team reached consensus on 10 general EDK items applicable to commonly prescribed drugs (Table 1).

DISCUSSION

With today's increasing access to online information resources (e.g., national formularies, guidelines, eBooks), it is no longer clear what ready drug knowledge doctors should have or what they can look up. This is the first study to determine Essential Drug Knowledge, i.e. information about commonly prescribed drugs that junior doctors must know in order to prescribe rationally. After a two-phase Delphi study with three commonly prescribed drugs, the research team generated a list of 10 general EDK items. We plan to add additional drugs from the top 10 most frequently prescribed drugs to validate the EDK list for all commonly prescribed drugs.

Questionnaire methodology

To improve the Delphi methodology, we (1) recruited experts from various practice settings and specialties, to reflect the general population of doctors in primary and secondary health care; (2) derived objective data from the national drug formulary and allowed participants to comment on/add to the questionnaire content; (3) used a dichotomous scale and consensus cut-off of 80% agreement to develop a list of key items rather than one with additional items that would be ''nice to know''.

Interpretation of the results

Previous studies of required pharmacological knowledge of commonly prescribed drugs have been mainly based on the expert opinion of either senior clinical pharmacologists[17,19] or local formularies and local teachers.[18,21] Only one study used a Delphi technique to determine required

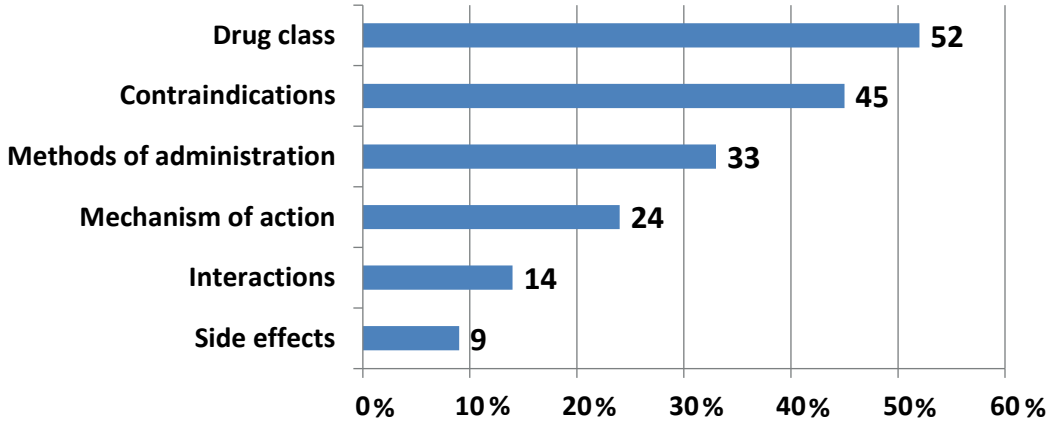

Figure 2. Essential Drug Knowledge divided in categories (% of initial items).

Table 1. Essential Drug Knowledge, including an example of another commonly prescribed drug.

Essential Drug Knowledge	Example: enalapril*
Drug class	
1. pharmacological and chemical subgroup	antihypertensive: ACE inhibitor†
2. appropriate indication(s) for use in primary health care	essential hypertension, congestive heart failure, renal protection
Pharmacological mechanism of action	
3. main mechanism of action (level of active substance)	inhibition of the renin-angiotensin-aldosterone system
Interactions	
4. interaction(s) at drug class level	NSAIDs‡, potassium sparing diuretics, potassium salts, diuretics
Contraindications	
6. contraindication(s) with clinically severe outcome 5. hypersensitivity reaction(s)	previous angioedema associated with ACE inhibitor, hypersensitivity to ACE inhibitor, pregnancy, angioedema, skin rash, itchiness
Side effects	
7. common side effect(s) (>1%) 8. severe or potentially lethal side effect(s) (<0.1%)	cough, dizziness, nausea, hyperkalaemia angioedema, anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis
Methods of administration	
9. common method(s) of administration	capsule, tablet
10. initial adult dose	2,5–20 milligrams daily

* included in the World Health Organization List of Essential Medicines 2011. † angiotensin-converting-enzyme inhibitor; ‡ non-steroidal anti-inflammatory.

pharmacological knowledge. Kilroy and Mooney provided a thorough overview of therapeutic agents that trainees should know about in order to practise safe clinical emergency medicine.[30] However, as in other studies, the overview provided a rather general and superficial description of what should be known about these drugs (e.g., 'know their side effects'). Earlier studies failed to clearly define what information students and doctors truly need to know in order to prescribe rationally. This study fills this gap and provides a more detailed list of information that students and junior doctors should know. This list further adds to a recent Delphi study describing core competencies in basic and clinical pharmacology for newly qualified physicians.[31] Our EDK list could be incorporated into our national medical curricula to help medical students learn drug facts during their education and training and could be used to develop prescribing assessments that test drug knowledge relevant to clinical practice. Although we primarily focused on junior doctors, our list might also be useful for life-long learning and knowledge maintenance of more experienced physicians. However, rational prescribing is not solely based on knowledge – it also requires judgement and prescribing skills.[32] Thus medical curricula should not only focus on the acquisition of pharmacology and pharmacotherapy knowledge but also on the provision of adequate training

in prescribing skills, for example by using the WHO 6-step method.[33] In this method, basic pharmacology knowledge has to be accurately applied to specific patient characteristics (e.g., changed pharmacokinetics). Thus in order to learn prescribing skills, students need to have an understanding of basic pharmacology. This aspect is not covered by list of EDK presented in this study. Interestingly, whereas previous studies suggested that it was not necessary for junior doctors to know exact drug doses by heart, [19,21] the experts in our study considered it essential that junior doctors should know the 'initial adult dose' of a drug. This might be because experienced doctors are aware that poor knowledge of drug dosages is a frequent cause of prescribing errors.[1,3,9,11,16] Better training and practice in choosing the correct drug dose during medical training could be an important component of interventions to reduce prescribing errors; for example, by integrating prescribing training in clinical practice.[2,34]

The finding that knowledge of drug class was considered the most important category of EDK (53%) is not surprising. Doctors need to know the drug class in order to be able to recall and select a particular drug. However, it is notable that knowledge of drug–disease contraindications was considered the second most important category (45%). A possible explanation for this is that, unlike drug–drug interactions for example, drug–disease contraindications are less likely to be detected by clinical decision support systems.[35] Thus when prescribing drugs, doctors need to actively check for contraindications based on pre-existing morbidities and other patient-related conditions. This requires a broader knowledge base. Moreover, a possible reason why the experts considered knowledge of drug–drug interactions relatively less important (14%) is that doctors rely on electronic support systems when checking for drug–drug interactions. However, we think that prescribers should not rely too heavily on clinical support systems, but should actively verify the suitability of drug treatment for the individual patient (i.e., checking for both contraindications and interactions) in order to prescribe rationally.[36] We think that medical curricula should put more emphasis on learning how to apply knowledge of drug interactions and contraindications, especially in acute prescribing situations.

Limitations

Our study had some methodological limitations. First, the number of experts who agreed to participate in the study was lower than expected; however, our panel corresponded with the typical sample size for Delphi studies of 15–20 participants.[37] Second, the three drugs chosen may not have adequately captured the scope of knowledge applicable to the larger number of commonly prescribed drugs (approximately 80–100). Third, the results might not be generalizable to other countries, where drugs other than the three chosen here may be among the most commonly prescribed. However, since two of the studied drugs are included in the World Health Organization List of essential medicines,[27] we think that our list would be useful and applicable to prescribing training in medical schools outside the Netherlands. Fourth, the experts' own level of knowledge might have influenced their choice of EDK for junior doctors; however, because of the detailed instructions they received this influence might be negligible. Lastly, the consultants and registrars per drug came from only one discipline. This might have introduced a selection bias. For example, cardiologists might overrate the risk of hypokalaemia since they frequently prescribe a higher dose

of hydrochlorothiazide. It would have been more appropriate if consultants and registrars from all three disciplines evaluated each drug. However, we expected this approach to be time-consuming, which might have decreased the response rate.

CONCLUSIONS

This is the first study to address what information junior doctors should know about the drugs they frequently prescribe. We identified a list of EDK items that could be used in the development of curricula and training programmes, and for assessing the prescribing competence of future junior doctors. Although this is an important first step, further research is needed to evaluate the generalizability of this list to other commonly prescribed drugs. Moreover, experts from different specialties need to be included to validate our findings. It would also be interesting to investigate why our experts think that this specific EDK is crucial for junior doctors.

ACKNOWLEDGEMENTS

We are grateful to all the doctors who participated in the study and responded to our questionnaire.

REFERENCES

1. Dornan T, Ashcroft D, Heathfield H, et al. An indepth investigation into causes of prescribing errors by foundation trainees in relation to their medical education: EQUIP study. Final report for the GMC, December 2009. Available at: http://www.gmc-uk.org/FINAL_Report_prevalence_and_causes_of_prescribing_errors.pdf_28935150.pdf.
2. McLellan L, Tully MP, Dornan T. How could undergraduate education prepare new graduates to be safer prescribers? Br J Clin Pharmacol. 2012;74(4):605–613.
3. Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospitals inpatients. A prospective study. Lancet. 2002;359(9315):1373–1378.
4. Celebi N, Weyrich P, Riessen R, Kirchhoff K, Lammerding-Koppel M. Problem-based training for medical students reduces common prescription errors: a randomised controlled trial. Med Educ. 2009;43(10):1010–1018.
5. McCarthy RM, Hilmer SN. Teaching junior medical officers safe and effective prescribing. Intern Med J. 2013;43(11):1250–1253.
6. Ross S, Ryan C, Duncan EM, et al. Perceived causes of prescribing errors by junior doctors in hospital inpatients: a study from the PROTECT programme. BMJ Qual Saf. 2013;22(2):97–102.
7. Kopp BJ, Erstad BL, Allen ME, Theodorou AA, Priestley G. Medication errors and adverse drug events in an intensive care unit: direct observation approach for detection. Critical Care Medicine. 2006;34(2):415–425.
8. Kraenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf. 2007;30(5):379–407.
9. Coombes ID, Stowasser DA, Coombes JA, Mitchell C. Why do interns make prescribing errors? A qualitative study. Med J Aust. 2008;188(2):89–94.
10. Buckley MS, Erstad BL, Kopp BJ, Theodorou AA, Priestley G. Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. Pediatr Crit Care Med. 2007;8(2):145–152.
11. Lewis PJ, Ashcroft DM, Dornan T, Taylor D, Wass V, Tully MP. Exploring the causes of junior doctors' prescribing mistakes: a qualitative study. Br J Clin Pharmacol. 2014;78(2):310–319.
12. Duncan EM, Francis JJ, Johnston M, et al. Learning curves, taking instructions, and patient safety: using a theoretical domains framework in an interview study to investigate prescribing errors among trainee doctors. Implement Sci. 2012;7:86.
13. Tully MP, Ashcroft DM, Dornan T, Lewis PJ, Taylor D, Wass V. The causes of and factors associated with prescribing errors in hospital inpatients: A systematic review. Drug Saf. 2009;32(10):819–836.
14. Agrawal A, Aronson JK, Britten N, et al. Medication errors: problems and recommendations from a consensus meeting. Br J Clin Pharmacol. 2009;67(6):592–598.
15. Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care. 2002;11(4):340–344.
16. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995;274(1):35–43.
17. Orme M, Frolich J, Vrhovac B. Towards a core curriculum in clinical pharmacology for undergraduate medical students in Europe. Eur J Clin Pharmacol. 2002;58(9):635–640.
18. Maxwell S, McQueen DS, Ellaway R. eDrug: a dynamic interactive electronic drug formulary for medical students. Br J Clin Pharmacol. 2006;62(6):673–681.
19. Maxwell S, Walley T. Teaching safe and effective prescribing in UK medical schools: a core curriculum for tomorrow's doctors. Br J Clin Pharmacol. 2003;55(6):496–503.

20. De Vries TP, Daniels JM, Mulder CW, et al. Should medical students learn to develop a personal formulary? An international, multicentre, randomised controlled study. Eur J Clin Pharmacol. 2008;64(6):641–646.
21. Ross S, Maxwell S. Prescribing and the core curriculum for tomorrow's doctors: BPS curriculum in clinical pharmacology and prescribing for medical students. Br J Clin Pharmacol. 2012;74(4):644–661.
22. Dunn WR, Hamilton DD, Harden RM. Techniques of identifying competencies needed of doctors. Med Teach. 1985;7(1):15–25.
23. Linstone HA, Turoff M. The Delphi method: techniques and applications. London: Addison-Wesley Publishing Company; 1975.
24. Clayton M. Delphi: a technique to harness expert opinion for critical decision making tasks in education. Educ Psychol-UK. 1997;17(4):373–386.
25. Wijnen-Meijer M, van der Schaaf M, Nillesen K, Harendza S, Ten Cate O. Essential facets of competence that enable trust in graduates: A Delphi study among physician educators in the Netherlands. J Grad Med Educ. 2013;5(1):46–53.
26. Griens AM, Janssen JM, Kroon JDL, Lukaart JS, van der Vaart RJ. Data en feiten 2014: het jaar 2013 in cijfers. Den Haag: Stichting Farmaceutische Kengetallen; 2014.
27. WHO Model List of Essential medicine 17th list, 2011. Available at: http://apps.who.int/iris/bitstream/10665/70640/1/a95053_eng.pdf.
28. van Loenen AC. Farmacotherapeutisch Kompas 2012. Amstelveen: College voor zorgverzekeringen; 2012.
29. van Unen RJ, Tichelaar J, Nanayakkara PW, van Agtmael MA, Richir MC, de Vries TP. A Delphi study among internal medicine clinicians to determine which therapeutic information is essential to record in a medical record. J Clin Pharmacol. 2015;55(12):1415-1421.
30. Kilroy DA, Mooney JS. Determination of required pharmacological knowledge for clinical practice in emergency medicine using a modified Delphi technique. Emerg Med J. 2007; 24(9):645–647.
31. Midlöv P, Höglund P, Eriksson T, Diehl A, Edgren G. Developing a competency-based curriculum in basic and clinical pharmacology – A Delphi study among physicians. Basic Clin Pharmacol Toxicol. 2015;117(6):413–420.
32. Aronson JK, Henderson G, Webb DJ, Rawlins MD. A prescription for better prescribing. BMJ. 2006;333(7566):459–460.
33. De Vries TP, Henning RH, Hogerzeil HV, Fresle DA. Guide to good prescribing. Geneva: World Health Organization; 1994.
34. Tichelaar J, van Kan C, van Unen RJ, et al. The effect of different levels of realism of context learning on the prescribing competencies of medical students during the clinical clerkship in internal medicine: an exploratory study. Eur J Clin Pharmacol. 2015;71(2):237–242.
35. Tora H, Bo H, Bodil L, Goran P, Birgit E. Potential drug related problems detected by electronic expert support system in patients with multi-dose drug dispensing. Int J Clin Pharm. 2014;36(5):943–952.
36. Brinkman DJ, Tichelaar J, van Agtmael MA, de Vries TP, Richir MC. Self-reported confidence in prescribing skills correlates poorly with assessed competence in fourth-year medical students. J Clin Pharmacol. 2015;55(7):825–830.
37. Ludwig B. Predicting the future: have you considered using the Delphi methodology? J Ext. 1997;35(5):1–4.

APPENDIX 1

EDK items for which there was ≥80% agreement among experts. In order to be a rational prescriber, a junior doctor should have a thorough knowledge of the following drug information.

EDK item	%
Amoxicillin	
1. Drug class	
Amoxicillin is a broad-spectrum antibiotic	100
Amoxicillin is used to treat susceptible Gram-positive and Gram-negative bacteria	92
Amoxicillin is an antibiotic in the aminopenicillin family	89
2. Pharmacological mechanism of action	
Amoxicillin contains a -lactam ring	88.2*
Amoxicillin reaches therapeutic levels in mucosa	88.2*
Penicillinase-forming strains of Staphylococcus aureus are resistant to amoxicillin	88
3. Interactions	
-	-
4. Contraindications	
Hypersensitivity to penicillin	100
Hypersensitivity to cephalosporin	92
Amoxicillin enters breast milk in low amounts but does not lead to a significant risk for the baby	88.2*
Mononucleosis infectiosa, due to increased risk of skin rash	88
Amoxicillin can be safely used during pregnancy	88
5. Side effects	
A common side effect (1–10%) of amoxicillin is allergic skin rash	100
A rare side effect (0.01–0.1%) of amoxicillin is a severe (potentially lethal) anaphylactic reaction	100*
A common side effect (1–10%) of amoxicillin is gastrointestinal discomfort	96
Amoxicillin leads to an increased risk for yeast growth (e.g., candidiasis)	94.1**
A common side effect (1–10%) of amoxicillin is nausea	84
A rare side effect (0.01–0.1%) of amoxicillin is angioedema	82.4*
A common side effect (1–10%) of amoxicillin is vomiting	81
6. Methods of administration	
Clinical improvement should be seen within 24–48 hours of amoxicillin initiation	100**
Amoxicillin is the drug of preference in the aminopenicillin family because of its good reabsorption and low dose frequency	92
Compliance with antibiotics is often low	88.2**
Amoxicillin should be continued for 48–72 hours after clinical symptoms have resolved	88
Amoxicillin can be administered orally as a tablet	88
Amoxicillin can be administered orally as a capsule	85*
Amoxicillin can be administered orally as a suspension	84
Standard dosage for adults, teenagers, and children 10 years of age and older: 350 to 1000 mg every 8 hours,	82.4*
depending on the national antimicrobial resistance of Streptococcus pneumoniae# Amoxicillin can be administered by injection	80
Hydrochlorothiazide	
1. Drug class	
Hydrochlorothiazide is a thiazide diuretic	100

Appendix 1. (continued)

EDK item	%
Indication for hydrochlorothiazide: arterial hypertension	92.3
Indication for hydrochlorothiazide: stable, chronic, mild to moderate heart failure (NYHA II or III)	84.6
2. Pharmacological mechanism of action	
Duration of action of hydrochlorothiazide is 10–12 hours	85.7
3. Interactions	
Hydrochlorothiazide can increase the effect of other antihypertensive drugs	88.5
Hydrochlorothiazide should be stopped 2–3 days before starting an ACE inhibitor or the dosage should be reduced to avoid first-dose hypotension	85.7*
4. Contraindications	
Anuria	96.2
Severe kidney failure (creatinine clearance <30 ml/min)	92.3
Hypersensitivity to thiazide diuretics	92.3
Conditions associated with increased potassium loss (e.g., salt wasting nephropathy)	88.5
Hyponatraemia	84.6
Caution is advised in patients with a history of gout	84.6
Refractory hypokalaemia	80.8
Prerenal (cardiogenic) kidney injury	80.8
5. Side effects	
A rare side effect (0.01-0.1%) of hydrochlorothiazide 12,5 mg is hypokalaemia#	100
A rare side effect (0.01-0.1%) of hydrochlorothiazide is orthostatic hypotension	92.3
A rare side effect (0.01-0.1%) of hydrochlorothiazide is hyponatraemia	84.6
6. Methods of administration	
Hypertension: initial dose 12.5–25 mg daily	100
Take a single daily dose of ≤50 mg preferably in the morning	92.3
Serum electrolytes (in particular potassium) need to be monitored 3–4 weeks after onset of treatment, and then every 4–6 months	92.3
Oedema: initial dose 12.5–25 mg daily	90.5*
Heart failure: initial dose 25–50 mg daily	80.8
Diclofenac	
1. Drug class	
Diclofenac belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs)	100
Indication: degenerative joint diseases	100
Indication: acute low back pain	100
Indication: rheumatoid arthritis	97.5
Indication: painful postoperative and post-traumatic inflammation and swelling (e.g., dental or orthopaedic)	92.1
Indication: myalgia	89.5
Indication: frozen shoulder (periarthritis humeroscapularis)	82.6*
Indication: headache	82.6*
2. Pharmacological mechanism of action	
Diclofenac has an analgesic effect	100
Diclofenac is a prostaglandin synthesis inhibitor	92.1
Diclofenac inhibits platelet aggregation	91.3*
Diclofenac has an antipyretic effect	91.3*

Appendix 1. (continued)

EDK item	%
Diclofenac has an antiphlogistic effect	81.6
3. Interactions	
Combined use with oral anticoagulants may prolong prothrombin time	95.7*
Gastrointestinal side effects may be potentiated by concomitant use with other prostaglandin synthesis inhibitors	95.7*
Gastrointestinal side effects may be potentiated by concomitant use with corticosteroids	81.6
4. Contraindications	
4.1 Absolute contraindications	
Stomach and/or duodenal ulceration or gastrointestinal bleeding, active or in history	100
Gastrointestinal bleeding or perforation resulting from use of prostaglandin synthesis inhibitors	100
Renal insufficiency (glomerular filtration rate <30 ml/min)	100
Severe heart failure	97.4
Angioedema after use of diclofenac	94.7
Cerebrovascular haemorrhage	92.1
Urticaria after use of diclofenac	92.1
Asthma attack after use of diclofenac	89.5
Severe cirrhosis of the liver	86.8
Ulcerative colitis	86.8
History of, or active, blood dyscrasias	82.6*
4.2 Relative contraindications (caution advised)	
Increased risk of gastrointestinal complications	100
Blood clotting disorders	94.7
Elderly patients	86.8*
Ischaemic heart diseases	86.8
History of cerebral haemorrhage	86.8
Crohn's disease	82.6
Liver diseases	82.6*
Hypertension	82.6*
5. Side effects	
A common side effect (1–10%) of diclofenac is nausea and vomiting	95.7*
A rare side effect (0.01–0.1%) of diclofenac is gastrointestinal ulceration (with or without bleeding and perforation)	87*
A common side effect (1–10%) of diclofenac is dyspepsia	81.6
Caution is advised in older patients because of a higher risk of cardiovascular morbidity and mortality#	-
6. Methods of administration	
Monitoring of blood counts, liver and renal functions is recommended when prescribing for a longer period	89.5
Stop treatment at the first appearance of skin rash, mucosal lesions or any other symptom of hypersensitivity	86.8
Dosage rheumatoid arthritis/osteoarthritis/periarthritis humeroscapularis: adults, initial dose 100–150 mg in 2–3 divided doses daily	82.6*

* items that achieved agreement in Round 2; ** new items added by respondents; # adapted by the reviewers.
2 items regarding amoxicillin were removed by the reviewers: "Amoxicillin can reduce the efficacy of oral conceptive drugs", and "Severe infections require intravenous administration of amoxicillin".