European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:675–681
https://doi.org/10.1007/s10096-019-03473-7

ORIGINAL ARTICLE

Macrolide prescription in Dutch children: compliance with guidelines

Rosa A. M. Bandell[1,2] · Tanja Dekkers[3] · Bernardus A. Semmekrot[1] · Saskia N. de Wildt[4,5] · Hanneke W. H. A. Fleuren[2] · Margaretha F. Warlé-van Herwaarden[6] · Peter Füssenich[7] · Gerardus P. Gerrits[1] · Cornelis Kramers[2,4]

Received: 2 October 2018 / Accepted: 2 January 2019 / Published online: 24 January 2019

Abstract

For reasons of antibiotic resistance and side effects, macrolides should be prescribed with care in the pediatric population. We evaluated the adherence to Dutch guidelines of macrolide prescription in children and estimated the risk of *Mycoplasma pneumoniae*–associated pneumonia based on Fischer's decision tree. In this retrospective study, we included children aged 0–18 years who were treated with azithromycin or clarithromycin for pulmonary disease in four settings from general practice to hospital ward for (1) the prescriptions not in accordance with the guideline of the Dutch Association of Pediatrics and (2) the risk of *M. pneumoniae* in patients with community-acquired pneumonia (CAP) according to Fischer's decision tree. The latter suggests that children older than three years with a fever lasting more than two days are at high risk for *M. pneumoniae* and that it is therefore justified to treat them with macrolides. In total, 189 macrolide prescriptions from 2015 until 2017 were analyzed: 139 children used macrolides for a pulmonary indication (75%); 18% ($n = 25$) of the prescriptions were not in accordance with Dutch guidelines. Only 9.1% of patients with CAP were classified as having a high risk of *M. pneumoniae* according to Fischer's decision tree. A significant proportion of macrolide prescriptions for Dutch children with a pulmonary disease appears not to be in accordance with the guidelines. Most patients with CAP treated with a macrolide actually had a low risk of having *M. pneumoniae* according to Fischer's decision tree. Both observations suggest overuse of macrolides in children.

Keywords Microbiology · Respiratory disorders · Pharmacology · Infectious disease medicine

Introduction

Macrolide antibiotics are frequently prescribed to children in The Netherlands. In 2015, oral macrolides were prescribed to 85,700 children under 15 years of age and to another 59,537 teenagers and young adults under 25 [1], accounting for 29% of all macrolide prescriptions in The Netherlands in that year [2]. Such large-scale use of macrolides can give rise to several side effects. One of the most important and potentially dangerous side effects is prolongation of the QT interval, which, on rare occasions, results in the occurrence of life-threatening arrhythmias. The risk of prolongation of the QT interval is much less studied in children than in adults and is still inconclusive [3–13], although azithromycin seems to be safer than clarithromycin and erythromycin in this respect [14–17]. Furthermore, worldwide extensive macrolide use has led to an increase in the prevalence of macrolide-resistant *Mycoplasma pneumoniae*. Resistance rates range from 97% in China to 0–2% in Northern Europe [18].

There are several indications for prescribing macrolide antibiotics to children [19]. In pediatric care, the majority of macrolides are applied to treat respiratory infections [18–24]. Other indications include neonatal chlamydia infections, acute otitis media, eradication of *Helicobacter pylori* infection, prophylaxis after tick bite or erythema migrans,

✉ Rosa A. M. Bandell
r.bandell@gmail.com

1 Department of Pediatrics, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands

2 Department of Clinical Pharmacy, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

3 Department of Internal Medicine, Radboudumc, Nijmegen, The Netherlands

4 Department of Pharmacology-Toxicology, Radboudumc, Nijmegen, The Netherlands

5 Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia, Rotterdam, The Netherlands

6 Community Pharmacy, Groesbeek, The Netherlands

7 General Practice, Füssenich and Dral, Groesbeek, The Netherlands

and cystic fibrosis [19, 25]. Besides antibacterial effects, macrolides may have immune-modulatory effects [26, 27]. For this reason, numbers of prescriptions are increasing in the treatment of wheezing illness and asthma, although not yet recommended in the Dutch guidelines [20, 26, 28–34].

Community-acquired pneumonia (CAP) is a clinical diagnosis in children presenting with a fever in combination with increased respiratory rate and breathing effort. Children with a clinically evident CAP should receive antibiotics according to the Dutch Association of Pediatrics [35]. This guideline recommends amoxicillin as the first-choice treatment for CAP, since it is generally well tolerated and effective against the majority of CAP-associated pathogens in children in The Netherlands [35]. Macrolides are recommended in case of (1) amoxicillin allergy/intolerability, (2) proven or strong clinical suspicion of infection with *M. pneumoniae* or *Chlamydia pneumoniae*, and (3) in addition to amoxicillin in case of insufficient response to initial therapy [35]. The use of oral macrolides for CAP in Dutch children is basically confined to azithromycin and clarithromycin, as these two agents are more stable, better absorbed, and better tolerated than erythromycin [12, 19].

The use of macrolides in case of an atypical CAP is based on clinical suspicion, and therefore empirical. Since symptoms and radiological signs are not specific for *M. pneumoniae* infection, and PCR and serologic reactions cannot discriminate between acute *M. pneumoniae* infection or chronic carriage, it is very difficult to differentiate between a typical and atypical CAP [18, 36]. Previous research by Fischer et al. shows that especially children older than three years with more than two days of fever are at risk for an atypical pneumonia by *M. pneumoniae* (Fig.. 1a). Using this simple clinical decision rule could help physicians (mostly pediatricians and general practitioners) in their choice to empirically start macrolide treatment. Fischer et al. advise to initially treat only these "high-risk" children with macrolides [18, 37, 38].

Currently, the number of macrolide prescriptions per indication in The Netherlands is unclear. In patients suffering from CAP, the diagnostic uncertainty about *M. pneumoniae*, as previously discussed, can lead to inappropriate antibiotic prescribing [36]. Considering the current evidence concerning antibiotic resistance and QT prolongation, limited use of macrolide in children seems wise. For this reason, we assessed the treatment indications for macrolide prescriptions in four different pediatric settings (general practice, emergency department, outpatient department, and pediatric ward), in order to identify potential unwarranted macrolide prescription in pulmonary pediatric care. Also, we assessed the frequency of the parameter "high risk of *M. pneumoniae* infection" according to Fischer's decision tree in children with CAP treated with a macrolide antibiotic (Fig. 1a).

Materials and methods

Patients

In a retrospective study, we included children aged 0–18 years treated with azithromycin or clarithromycin in the period from January 2015 until January 2017. All children who received azithromycin or clarithromycin were identified from the following: Department of Pharmacy, Canisius Wilhelmina

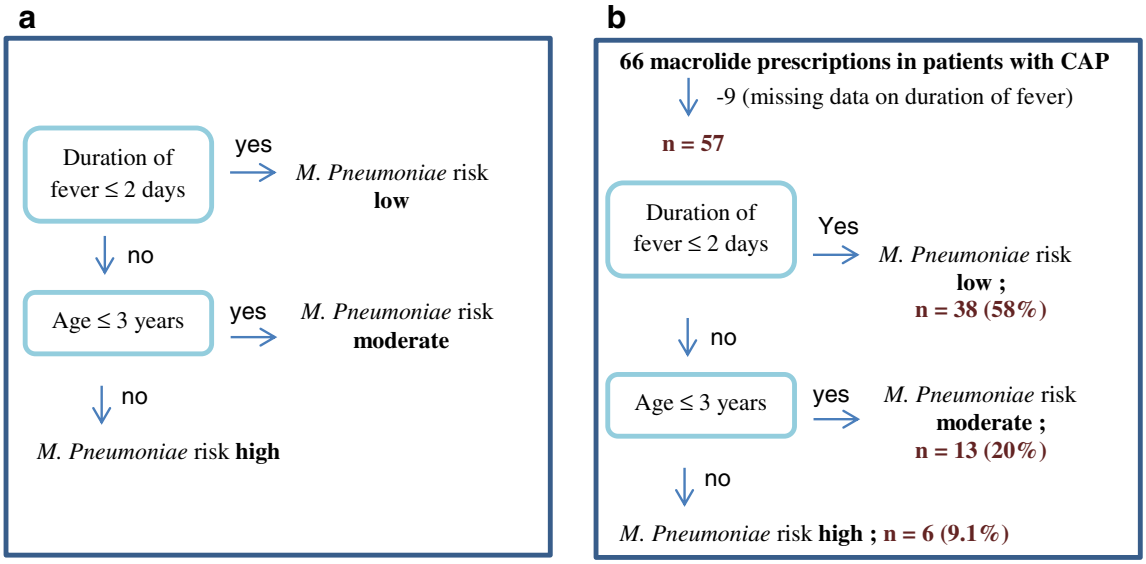

Fig. 1 **a** Clinical decision tree proposed by Fischer et al. (2002) for ruling out *M. pneumoniae* infection in children with community-acquired pneumonia [37]. Fischer et al. advise to initially treat only the "high-risk" children with macrolides. **b** Risk of *M. pneumoniae* infection according to Fischer's decision tree in 66 patients with CAP

Hospital (CWZ); Department of Clinical Pharmacy, CWZ; an emergency pharmacy in Nijmegen; and a local pharmacy in Groesbeek. Based on electronic medical records, patients were included in the study if antibiotics were prescribed for a pulmonary reason. Three of the four pediatric settings were in a Dutch primary hospital in Nijmegen (CWZ): the pediatric ward ($n = 94$, 68%), outpatient department ($n = 20$, 14%), and emergency department ($n = 11$, 7.9%). Children from the fourth setting got their prescription from one of six prescribing general practitioners (GPs) in the village of Groesbeek ($n = 14$, 10%).

Data collection

Based on the antibiotic prescriptions from the four pharmacies, we collected data from electronic medical files (from CWZ and from six GPs). We collected information on the following variables: gender, age, comorbidity (including atopy), medication use, laboratory results (blood count, minerals, CRP), radiological imaging, and spirometry results.

Medical files were analyzed for two purposes. First, we wanted to determine whether macrolide treatment was in accordance with the Dutch guidelines [33, 34]. The judgment was done by two pediatricians (E.C. and J.Z.-V., acknowledging contributors), independent of one another. The pediatricians were not involved in either patient care in CWZ or the Groesbeek GPs, to ensure their independence. If the judgment of these pediatricians deviated (which occurred in 18 cases), consensus was reached in a separate meeting.

The second outcome was the number of children with CAP having the parameter "high risk of *M. pneumoniae* infection" according to Fischer's decision tree, i.e., children with CAP being older than three years with more than two days of fever.

Statistical analyses

Data were collected using the eCRF software Castor. Statistical analyses were performed with IBM SPSS version 20. Continuous variables were analyzed for significant differences in the four different settings by ANOVA test in the case of a normal distribution. When variables did not meet the one-way ANOVA normality assumption, Kruskal-Wallis test was performed. Categorical variables were analyzed by Pearson's chi-squared test or, in the case of small numbers, Fisher's exact test. For associations with unjustified prescriptions, a multivariate logistic regression analysis containing the univariate significant variables ($p < 0.10$) was used, and odds ratios were determined for the effect size. Inter-rater agreement was measured by interobserver kappa.

Ethics

The regional Medical Ethical Committee Nijmegen-Arnhem waived the need for ethical approval, according to the Dutch Medical Research Involving Human Subjects Acts, since only patient chart data were collected. The study has been conducted in accordance with the Personal Data Protection Act.

Results and discussion

Patients, prescriptions, and indications

A total of 189 macrolide prescriptions were analyzed. The indications for macrolides in children showed a large variation in the four settings ($p < 0.05$, Fig. 2).

In 59% of all prescriptions, CAP was (one of) the reason(s) for prescribing the antibiotic. In 22% of prescriptions, a combination of indications (in differential diagnosis) was reason to start the macrolide antibiotic. In the majority of cases, it concerned viral wheeze in combination with CAP, and asthma exacerbation in combination with CAP (both $n = 13$, 32%). One hundred thirty nine children used azithromycin or clarithromycin for one of the following pulmonary indications (75%): CAP, pertussis, viral wheeze, asthma exacerbation, upper respiratory tract infection, or a combination. When focusing on these indications, some baseline characteristics were significantly different between the four settings (Table 1). For instance, younger children were more frequently admitted to the hospital than older children. Of all 139 prescriptions for a pulmonary indication, 108 concerned azithromycin (78%) and 31 clarithromycin (22%). The distribution of azithromycin and clarithromycin prescriptions did not differ significantly by pediatric setting ($p = 0.380$).

Outcomes

Adherence to Dutch pediatric guidelines

Table 2 shows the conclusions of the reviews of the two pediatricians assessing the patient files of all patients with a pulmonary indication for azithromycin or clarithromycin ($n = 139$). The interobserver kappa was 0.587. In total, 25 (18%) prescriptions were not in accordance with the guidelines, according to the two reviewing pediatricians (for example, there was no evident suspicion of an atypical microorganism, or no evident CAP). Four of these 25 prescriptions (16%) were written because of viral wheeze ($n = 2$) or asthma exacerbation ($n = 2$), aiming at the possible immune-modulatory effect of macrolide antibiotics [11, 12].

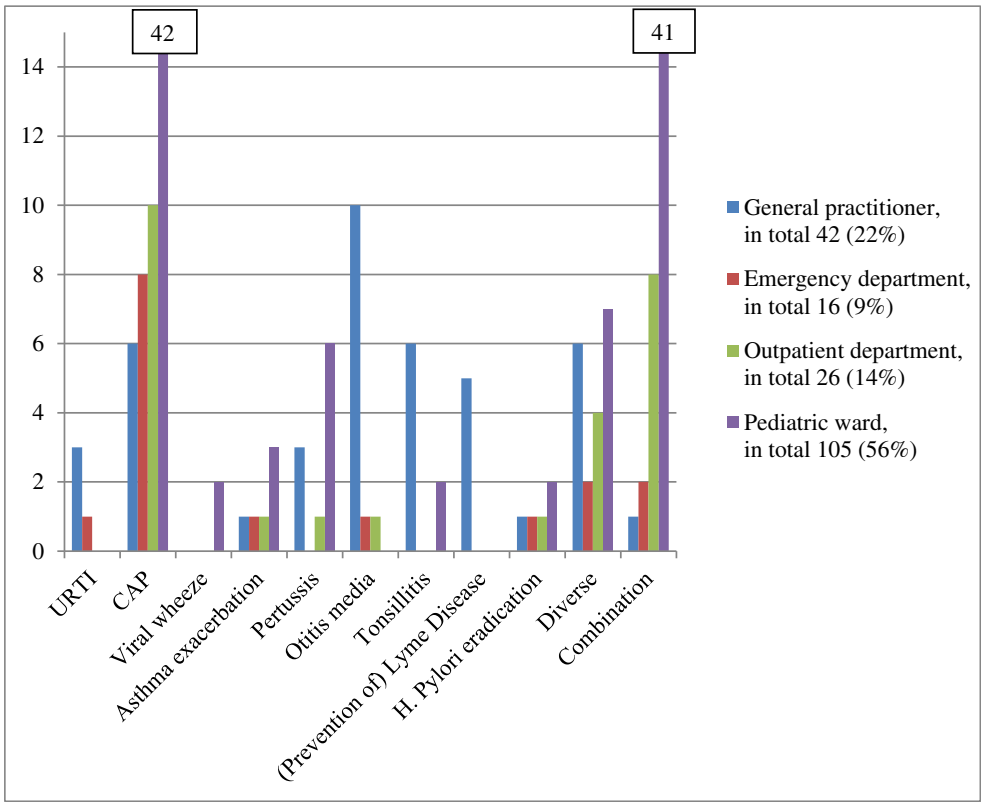

Fig. 2 All indications for azithromycin and clarithromycin in four pediatric settings. URTI, upper respiratory tract infection; CAP, community-acquired pneumonia; (Prevention of) Lyme Disease, both prophylaxis after a tick bite and in case of erythema migrans; H. Pylori, *Helicobacter pylori*; Diverse, included patients suffering from *Chlamydia trachomatis* infection, a provocation test for possible azithromycin allergy, lymphadenitis colli, skin problems, emerging sickle cell crisis, pleurodynia in a proven *M. pneumoniae* infection (serology), and, among other things, no availability of other antibiotics; Combination, included patients who had two or more indications in differential diagnosis

The highest proportion of unwarranted macrolide prescription was seen in general practice: 64% (9 of 14) of prescriptions by GPs for pulmonary diagnoses was not in accordance with Dutch guidelines ($p < 0.001$). This suggests that actions to improve inappropriate macrolide prescription should primarily aim at prescribing customs in general practice.

Table 1 Baseline characteristics of children with a pulmonary indication for azithromycin or clarithromycin

Prescriptions	Setting					
	General practitioner $n = 14$ (10%)	Emergency department $n = 11$ (8%)	Outpatient department $n = 20$ (14%)	Pediatric ward $n = 94$ (68%)	Total $n = 139$ (100%)	Sign.
Patient characteristics						
Male sex	4 (29%)	2 (18%)	12 (60%)	44 (47%)	62 (45%)	0.083
Mean age (years)	6.1 (4.3)	7.1 (5.6)	7.4 (4.8)	3.9 (3.7)	4.9 (3.7)	0.003
Medical history						
Atopy*	7 (50%)	2 (18%)	10 (50%)	27 (29%)	46 (33%)	0.098
Asthma	1 (7.1%)	2 (18%)	12 (60%)	16 (17%)	31 (22%)	< 0.001
Amoxicillin allergy/intolerance**	1 (7.1%)	2 (18%)	0 (0.0%)	6 (6.4%)	9 (6.5%)	0.274
Prescription information						
Azithromycin (vs. clarithromycin)	11 (79%)	7 (64%)	18 (90%)	72 (77%)	108 (78%)	0.380
Macrolide prescribed at first presentation	7 (50%)	8 (73%)	16 (80%)	37 (39%)	68 (49%)	0.003
Days to prescription after first presentation	8.7 (6.9)	3.7 (2.1)	16.5 (10.5)	2.3 (2.3)	5.6 (16)	0.001
Another antibiotic first	4 (29%)	7 (64%)	2 (10%)	32 (34%)	45 (32%)	0.021
Culture result known	1 (7.1%)	0 (0.0%)	3 (16%)	9 (9.8%)	13 (9.6%)	0.093

Data are *n* (%) or mean (SD). *Allergic rhinitis, atopic dermatitis, or asthma in medical history. **Not necessarily proven allergy, but when it is seen as reason not to treat with amoxicillin. Pearson's chi-squared test, Fisher's exact test, ANOVA test, and Kruskal-Wallis test were performed where appropriate

Table 2 Prescription justification

		Setting				
		General practitioner	Emergency department	Outpatient department	Pediatric ward	Total
Justification	Not according to guidelines*	9 (64%)	2 (18%)	6 (30%)	8 (9%)	25 (18%)
	According to guidelines*	5 (36%)	9 (82%)	14 (70%)	86 (91%)	114 (82%)
Total		14	11	20	94	139

Data are *n* (column%). *Indication for macrolide prescription is (not) according to the guideline

When performing a univariate logistic regression analysis, unjustified prescription was associated with the variables "setting" ($p < 0.001$), "comorbidity" ($p = 0.050$), and "chest X-ray performed" ($p = 0.045$). The highest odds ratios were seen in children in the GP setting, with any comorbidity, and in whom chest X-rays were not performed. In multivariate logistic regression analysis, only the variable "setting" remained significant ($p < 0.001$). Prescription in general practice had an OR of 14.6 compared with pediatric ward ($p < 0.001$, CI 3.4–62.2), the setting with the lowest risk of unjustified prescription. The OR of the outpatient department (compared with the pediatric ward) was 3.8 ($p = 0.038$, CI 1.1–13.2). No significant difference occurred for the emergency department, as compared to the pediatric ward ($p = 0.268$).

Risk of *M. pneumoniae* infection according to Fischer's decision tree

Sixty-six prescriptions in patients with CAP remained, when excluding patients who first used amoxicillin without clinical effect and patients with an amoxicillin allergy or intolerance ($n = 26$ and $n = 7$, respectively). In 14% ($n = 9$) of all prescriptions, the decision tree could not be used because of missing data on duration of fever. From the remaining 57 prescriptions, only 6 patients (9.1%) had high risk for *M. pneumoniae* according to the decision tree of Fischer et al., 13 patients (20%) had moderate risk, and 38 (58%) had low risk (Fig. 1b). This suggests that the Dutch guidelines for macrolide prescribing result in too many children with CAP being treated with macrolide antibiotics. On the other hand, it is important to realize that Fischer's algorithm is based on a relatively small study. Fischer et al. found a *M. pneumoniae* infection in only 32 patients (from a population of 253 children, 13%), of which only 23 (72%) fell into the high-risk group according to the decision tree. In addition, the authors based their 72% sensitivity on antibody testing in paired serum samples (at baseline and 4-week follow-up), which might not be adequate for diagnosing infection (vs. carriage) [4, 22]. So either the Dutch guidelines are not strict enough regarding macrolide prescription or the algorithm of Fischer is not valid.

Discussion

Our study has several limitations. First, the retrospective study design reduced the reliability of prescribing criteria. To overcome this limitation, we had the justification assessment performed by two independent pediatricians. Nevertheless, the justification was dependent on the written text in the medical files, which is sometimes concise, especially in the GP setting. Another limitation of this study is the small sample size, with small prescribing numbers in three of the four groups (GP, emergency department, and outpatient department).

Despite its limitations, several conclusions can be drawn from this study. The highest percentage of inappropriate macrolide prescription was seen in general practice. In children with CAP, the Dutch guidelines advise to prescribe a macrolide in case of suspected infection with an atypical microorganism. No clear guidance is given, however, when to suspect an atypical infection. When applying Fischer's decision tree, the vast majority of patients using a macrolide do not meet the criteria for high risk of *M. pneumoniae*.

To conclude, a significant part of macrolide prescriptions (18%) for Dutch children is not in accordance with the guidelines. Most patients with CAP treated with a macrolide had a low risk of having *M. pneumoniae* according to Fischer's decision tree. Both observations suggest overuse of macrolides in children. In view of antibiotic stewardship, we advise a more critical consideration of indications to restrict the use of a macrolide antibiotic in case of suspected infection with *M. pneumoniae*. In addition, we feel that improved diagnostic tools for a *M. pneumoniae* infection would be very helpful to reduce the number of inappropriate prescriptions for a macrolide antibiotic in pediatric practice.

Acknowledgments

- Dr. E.A. Croonen (Radboudumc, Department of Pediatrics, Nijmegen, The Netherlands, and Canisius Wilhelmina Hospital, Department of Pediatrics, Nijmegen, The Netherlands)
- Mrs. J.C. Zoet-Verheul (Canisius Wilhelmina Hospital, Department of Pediatrics, Nijmegen, The Netherlands)
- Mrs. M.W.R.G. Lennertz (Canisius Wilhelmina Hospital, Department of Outpatient Pharmacy, Nijmegen, The Netherlands)
- Mr. J. Maliepaard (Pharmacy Nijmegen, The Netherlands)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The regional Medical Ethical Committee Nijmegen-Arnhem waived the need for ethical approval, according to the Dutch Medical Research Involving Human Subjects Acts, as only patient chart data were collected.

Informed consent No informed consent was required.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. GIPdatabank Zorginstituut Nederland (2016) Aantal gebruikers naar leeftijd en geslacht voor ATC-code J01FA: Macroliden in 2015. https://www.gipdatabank.nl/databank.asp?tabel=03-lftgesl&geg=gebr&item=J01FA. Accessed 22 May 2017
2. GIPdatabank Zorginstituut Nederland (2016). Aantal gebruikers 2011–2015 voor ATC-subgroep J01FA: Macroliden. https://www.gipdatabank.nl/databank.asp. Accessed 22 May 2017
3. Kezerashvili A, Khattak H, Barsky A, Nazari R, Fisher J (2007) Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. J Interv Card Electrophysiol 18(3):243–246
4. Huang B, Wu C, Hsia C, Chen CY (2007) Azithromycin-induced torsade de pointes. Pacing Clin Electrophysiol 30(12):1579–1582
5. Cheng Y, Nie X, Chen X et al (2015) The role of macrolide antibiotics in increasing cardiovascular risk. J Am Coll Cardiol 66(20): 2173–2184
6. Ray W, Murray K, Hall K, Arbogast P, Stein C (2012) Azithromycin and the risk of cardiovascular death. N Engl J Med 20366(17):1881–1890
7. Svanström H, Pasternak B, Hviid A (2013) Use of azithromycin and death from cardiovascular causes. N Engl J Med 368(18): 1704–1712
8. Trac M, Mcarthur E, Jandoc R et al (2016) Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ 188(7): 120–129
9. Maisch N, Kochupurackal J, Sin J (2014) Azithromycin and the risk of cardiovascular complications. J Pharm Pract 27(5):496–500
10. Goldstein L, Gabin A, Fawaz A et al (2015) Azithromycin is not associated with QT prolongation in hospitalized patients with community-acquired pneumonia. Pharmacoepidemiol Drug Saf 24(10):1042–1048
11. Hancox J, Hasnain M, Vieweg W, Crouse E, Baranchuk A (2013) Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. Ther Adv Infect Dis 1(5):155–165
12. Graziani A, Hooper D, Thorner A (2016) Azithromycin, clarithromycin, and telithromycin. UpToDate. https://www.uptodate.com/contents/azithromycin-clarithromycin-and-telithromycin?source=search_result&search=azithromycin%20erythromycin&selectedTitle=1~150#H19. Accessed 18 May 2017
13. Lu Z, Yuan J, Li M et al (2015) Cardiac risks associated with antibiotics: azithromycin and levofloxacin. Expert Opin Drug Saf 14(2):295–303
14. Espadas D, Castillo S, Moreno M, Escribano A (2016) Lack of effect of azithromycin on QT interval in children: a cohort study. Arch Dis Child 101(11):10796
15. Germanakis I, Galanakis E, Parthenakis F, Vardas P, Kalmanti M (2006) Clarithromycin treatment and QT prolongation in childhood. Acta Paediatr 95(12):1694–1696
16. Promphan W, Khongphatthanayothin A, Horchaiprasit K, Benjacholamas V (2003) Roxithromycin induced torsade de pointes in a patient with complex congenital heart disease and complete atrioventricular block. Pacing Clin Electrophysiol 26(6): 1424–1426
17. Tilelli J, Smith K, Pettignano R (2006) Life-threatening bradyarrhythmia after massive azithromycin overdose. Pharmacotherapy 26(1):147–150
18. Meyer Sauteur PM, Unger WW, Nadal D, Berger C, Vink C, van Rossum AM (2016) Infection with and carriage of Mycoplasma pneumoniae in children. Front Microbiol 7(329):1–12
19. Klein J (1997) History of macrolide use in pediatrics. Pediatr Infect Dis J 16(4):427–431
20. Filho LS, Pinto L, Stein R (2015) Use of macrolides in lung diseases: recent literature controversies. J Pediatr 91:52–60
21. Nederlands Kenniscentrum Farmacotherapie bij Kinderen (2017) Claritromycine, kinderformularium. https://www.kinderformularium.nl/geneesmiddel/311/claritromycine. Accessed 1 June 2017
22. Nederlands Kenniscentrum Farmacotherapie bij Kinderen (2017) Azitromycine, kinderformularium. https://www.kinderformularium.nl/geneesmiddel/309/azitromycine. Accessed 1 June 2017
23. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (2017) Azitromycine. https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2424.html. Accessed 1 June 2017
24. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (2016) Claritromycine. https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2347.html. Accessed 1 June 2017
25. Southern KW, Barker PM, Solis-Moya A, Patel L (2012) Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev 11
26. Wong E, Porter J, Edwards M, Johnston S (2014) The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med 2(8):657–670
27. Lin S, Lee W, Liang Y, Yan D, Cheng P, Kuo M (2011) Azithromycin inhibits IL-5 production of T helper type 2 cells from asthmatic children. Int Arch Allergy Immunol 156:179–186
28. Stokholm J, Chawes B, Vissing N et al (2016) Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 4:19–26
29. Gardiner SJ, Gavranich JB, Chang AB (2015) Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev 1
30. Raissy H, Blake K (2016) Macrolides for acute wheezing episodes in preschool children. Pediatr Allergy Immunol Pulmonol 29(2): 100–103
31. Bacharier L, Guilbert T, Mauger D et al (2015) Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA 314(19):2034–2044
32. Fleming-Dutra K, Friedman C, Hicks L (2016) Comments and respons: early azithromycin treatment to prevent severe lower respiratory tract illnesses in children. JAMA 315(19):2121–2122
33. Nederlands Huisartsen Genootschap (2017). Richtlijnen en Praktijk. https://www.nhg.org/richtlijnen-praktijk. Accessed 15 June 2017

34. Nederlandse Vereniging voor Kindergeneeskunde (2017). Richtlijnen overzicht. https://www.nvk.nl/Kwaliteit/Richtlijnenoverzicht.aspx. Accessed 15 June 2017
35. Terheggen-Lagro S, Vreede ID, Tuut M, et al (2015) NVK-richtlijn (guideline of the Dutch Association of Pediatrics). Richtlijn diagnostiek en behandeling van ongecompliceerde pneumonie bij kinderen in de tweede en derde lijn (guideline diagnostics and treatment of uncomplicated pneumonia in children in the second- and third-line). http://www.kindergeneeskunde-mca.nl/images/stories/medische_protocollen/pneumonierichtlijn2015.pdf. Accessed 15 June 2017
36. Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A (2012) Clinical symptoms and signs for the diagnosis of Mycoplasma pneumoniae in children and adolescents with community-acquired pneumonia. Cochrane Database Syst Rev 10
37. Fischer J, Steiner F, Zucol F et al (2002) Use of simple heuristics to target macrolide prescription in children with community-acquired pneumonia. Arch Pediatr Adolesc Med 156:1005–1008
38. Katsikopoulos K, Pachur T, Machery E, Wallin A (2008) From meehl to fast and frugal heuristics (and back): new insights into how to bridge the clinical-actuarial divide. Theory Psychol 18(4): 443–464