EML Application on bronchitis and bronchiolitis

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Background

The WHO Essential Medicine List (EML) lists the most efficacious and safe medicines to treat illnesses that are considered high priority, including antibiotics. However, most antibiotics were listed decades ago and a comprehensive review of all the antibiotics listed over the past 40 years has never been done. Given increasing concerns about overuse of antibiotics, the emergence of antimicrobial resistance and the need to guarantee prompt access to highly beneficial treatments, revising and updating the list is an important priority.

Applications for revisions to the Model List are accepted every 2 years and are by single agent. However, similarly to what has been done for cancer in 2015, a syndrome-based approach was agreed as the best option. We have revised the list based on common syndromes to date and have now done this for bronchitis and bronchiolitis. All potentially relevant antibiotics for use across low, middle and high-income countries, were considered. The working group and the EML Secretariat a priori reasoned on the guiding principles to prioritize the selection of antibiotics: safety and efficacy, resistance, feasibility, parsimony.

As in our previous work on the original 21 syndromes (1), this review of the evidence was supplemented by a systematic search and synthesis of clinical practice guidelines. We placed a relative high value on evidence and guideline recommendations that can be applicable to a majority of patients and settings. The proposal will be presented for review by the WHO Expert Committee. It is acknowledged that local antibiotic resistance patterns are critical when selecting antibiotics and must be given strong consideration.

Rationale to consider acute bronchitis and bronchiolitis infections for the EML

Acute bronchitis in a common respiratory syndrome that frequently leads to the prescription of antibiotics, particularly during peak periods of respiratory virus circulation such as in the fall and winter. Although infection is thought to trigger episodes, pathogens are often not identified. Bronchitis is characterized by a transient inflammation of the trachea and major bronchi and is diagnosed clinically on the basis of cough and may also include sputum production, dypnea, and wheezes. This chapter is limited to episodes of acute brochitis in persons (smokers and non-smokers) with no pre-existing respiratory disease. It is important to distinguish this syndrome from acute exacerbations of chronic obstructive pulmonary disease. Bronchiolitis is inflammation of the brochioles that occurs in young children and infants for which the cause is viral, predominantly respiratory syncytial virus (RSV). Symptoms include cough, fever, wheezing, and difficulty breathing.

Methods

Data search and retention of Systematic Review and Meta-analysis evidence

A search for systematic reviews and meta-analyses of antibiotic therapy for bronchitis and bronchiolitis was conducted. We searched for systematic reviews and meta-analyses of randomized controlled trials (RCTs) from 1996 to September 9, 2020 that reported comparisons between different antibiotics and/or antibiotic classes and/or comparisons to placebo for bronchitis and bronchiolitis. We did not apply language restrictions and searched three databases (MEDLINE/PubMed, EMBASE, Cochrane Database of Systematic Reviews). For relevant clinical practice guidelines (CPGs), a search of all databases was conducted.

Screening of titles and abstracts, full-texts, as well as subsequent data abstraction, was conducted independently and in duplicate, followed by consensus discussion where there was disagreement, and with third party adjudication if needed. Following the electronic database searching and prior to the initiation of the formal screening of citations, a calibration exercise to ensure that screeners were uniform in their screening approach was conducted. For data abstraction, our focus was on comparative effectiveness evidence and we retrieved data on all reported outcomes (primary and secondary) in which cumulative estimates were reported. We further included any instance of a reported outcome with only one RCT.

Ranking of Systematic Reviews and Meta-analyses

We ranked the quality of evidence for each systematic review and meta-analysis on the basis of the study characteristics included in the review and the conduct of the review itself. Individual study characteristics included aspects of internal validity, such as risk of bias, as well as precision, while the publication date was a function of the review itself. We used the following five variables to develop a score for each systematic review or meta-analysis in order to rank them on overall quality of evidence: i) the judged quality assessment of the systematic review's evidence taking into account author's assessment and our assessment using GRADE. Note, our judged quality assessment involved a global assessment that included issues around potential for risk of bias e.g. randomization, blinding, data loss, publication bias, heterogeneity of the study estimates, whether Risk of Bias (RoB) was assessed with a valid technique, study selection and abstraction/RoB performed in duplicate/independently, comprehensive literature search, possible conflict of interest) ii) sample size of studies where reported, iii) number of events where reported and particularly for categorical/dichotomous data, iv) number of studies per outcome, and v) publication year. The judged quality of evidence variable included abstracting the risk of bias and level of evidence assessments reported by authors (e.g. Cochrane's Risk of Bias tool, the Jadad 5-point scale, GRADE methods). Using the five variables, we assigned each variable (in duplicate and independently using consensus to address disagreement) a rating of either high, moderate, low, and very low for each variable and assigned an ordinal score (high= 1.0, moderate =0.75, low=0.5, very low= 0.25). We averaged the score for each review. We then ranked the studies based on these mean scores which we multiplied by 100 (i.e. percentage) for ease of comprehension.

In deciding upon the list of antibiotics, we considered all relevant outcomes reported in the systematic reviews on bronchitis and bronchiolitis. We gave more weight to patient important

outcomes, mild to moderate harms, and lastly surrogate markers. The latter was the most common type of outcome reported and patient important outcomes are rare in this area. The potential for serious adverse events, reported either within the systematic reviews or by external agencies such as the FDA, were given great consideration. Specific definitions for the outcomes varied depending on the systematic review and by the definitions used in the original studies. We provided definitions where available within the literature, as each eligible review was documented.

Search and retention of Clinical Practice Guidelines

We reviewed well accepted international CPGs. These included clinical practice guidelines from North America and Europe. We reasoned that clinical practice guidelines might offer complementary information on the use of antibiotics for bronchitis and bronchiolitis, particularly given the context of antibiotic resistance and for circumstances where RCTs in systematic reviews and meta-analyses were not designed to address superiority of one or more antibiotics compared to others. We defined clinical practice guidelines as documents that provide recommendations on the management of infectious disease syndromes and optimal AB use. These documents must have contained an explicit methodology section which provided sufficient detail of how they were developed, such as an explicit search strategy, evidence quality assessment, and the method used to make recommendations.

Ranking of Clinical Practice Guidelines

For our approach, we ranked the clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument, which is designed to evaluate the process of practice guideline development and the quality of reporting.(2) We used 11 of the 23 AGREE II items (see Appendix Table 1) as these were the only items pertinent to our objective. Standard AGREE II methodology for scoring was used where the maximum possible score is based on the number of items by the number of assessors, the minimum possible score based on the minimum score by the number of items by the number of assessors, and the scaling of domains to arrive at an overall percentage. We used two assessors for this step and judged a scaled percentage of ≤70% to be low, 71 to 79 to be moderate, and scores ≥ 80% to be high.

Bronchitis

Synopsis of published evidence

We identified 11 systematic reviews (3-13) of which 8 (3-10) were either exacebrations of COPD (3-8), bronchiectasis (9), exacerbations of asthma (10) and 1 evidence brief (11). Two systematic reviews were for acute bronchitis (12, 13) and were reviewed in detail.

The highest quality SR (score 0.725) was a 2017 Cochrane review (12) (17 RCTs, 5099 participants). Antibiotics included doxycycline, erythromycin, trimethoprim-sulfa, azithromycin, cefuroxime, amoxicillin, and amoxicillin-clavulanic (ref). There was no difference in clinical

improvements between antibiotic and placebo groups (11 studies, 3841 participants), RR 1.07, 95%CI 0.99 to 1.15). Participants given antibiotics were less likely to have a cough (4 RCTs with 275 participants, RR 0.64, 95%CI 0. 49 to 0.85) and night cough (4 studies with 538 participants, RR 0.67, 95%CI 0.54 to 0.83), however there was no difference in productive cough at follow up. A shorter cough duration (7 studies, 2776 participants) was observed with antibiotics, mean difference -0.46 days, 95%CI -0.87 to -0.04 days). There was a significant increase in adverse events in the antibiotic treated group (12 studies, 3496 participants, RR 1.20, 95%CI 1.05 to 1.36). Another SR of 9 RCTs with a total of 774 participants and over 276 smokers randomized patients to antibiotics (erythromycin trimethoprim-sulfa, or doxycycline) or placebo (13). A meta-analysis was not performed. The authors reported that antibiotics showed no overall benefit in 5 of 9 of the RCTs while adverse events occurred on average in 11% of participants in the placebo group and 16% in the antibiotic group.

Synopsis of guidelines

Although our search identified nine documents (14-22), only two (21, 22) met criteria for CPGs. The NICE (UK) guideline (score 62.2) recommends not routinely offering an antibiotic to treat an acute cough associated with acute bronchitis in patients who are not systemically unwell or at high risk for complications (21). The guidelines do suggest offering an immediate antibiotic if the patient is systemically very unwell at face to face examination. The guideline referred to the NICE guideline on pneumonia to consider a point of are C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it it not clear whether antibiotics should be precribed. If an antibiotic is to be prescribed, the NICE guidelines recommend doxycycline as the first choice antibiotic with amoxicillin and clarithromycin being alternative choices. For children and young adults, amoxicillin was recommended as the first choice. The practise guidelines by the American College of Physicians and Centers for Disease Control and PreventIon (score 68.5) do not recommend anibiotics for patients with acute bronchitis (22).

Antibiotics selected for EML for Acute Bronchitis:

Based on the RCT evidence and the CPGs, antibiotics are not recommended for acute bronchitis in otherwise healthy people.

Bronchiolitis

Synopsis of published evidence

We identified four systematic reviews (14, 23-25). However, one was for for children with lower respiratory tract infection (23) and one for children with a wet cough (24). We have summarized

two systematic reviews, one for acute bronchioltis (14) and the other for persistent cough and wheeze following bronchiolitis (25).

The 2014 Cochrane review by Farley et al (0.625 score) focused on antibiotics for bronchiolitis in children under two years of age (14), and was based on 7 RCTs and 824 participants. Heterogeneity precluded meta-analysis for some outcomes. No deaths were reported among the groups included in the 7 RCTs. There were 3 RCTs that when pooled showed no difference betwen antibiotics (azithromycin) and placebo (mean difference in days of supplemental oxygenation -0.20 (95%CI -0.72 to 0.33). The trials (350 participants) were small and the point estimates were all in keeping with a reduction in symptoms of less than one day. Three studies showed no difference between antibiotics (azithromycin) and placebo with respect to length of hospital stay (mean difference in days -0.58, 95%CI -1.18to 0.02), similarly point estimates were < 1 day. Two RCTs found no difference in symptom measures (antibiotics were intravenous ampillin, oral erythromycon, and control) with point estimates indicating more symptoms in those treated with antibiotics in one trial.

The Cochrane review by McCallum et al (score 0.6) included only 2 RCTs (249 participants) where no significant differences between antibiotics (azithromyin in one RCT and clarithroymin in the other) and placebo for children that had persistent symptoms at follow up, OR 0.69, 95%CI 0. 37 to 1.28, no significant difference for children re-hospitalized a 6 months (OR 0.54, 95%CI 0.05 to 6.21) and no effect for wheeze at six months (OR 0.47, 95%CI 0.06 to 3.95) (25).

Synopsis of guidelines

We identified 4 clinical practice guidelines for brochiolitis (26-29), of which one was a CPG that has since been updated (29). The American Association of Pediatrics (score 74.7) reccomends that antibiotics should not be used unless there is a concomitant bacterial infection or a strong suspicion of one (26). The guidelines outline that rates of serious bacterial infection in children with bronchiolotis are low. The Italian Inter-Society consensus CPG (score 70.8) specify as well that antibiotics are not to be used routinely because of the risk for side effects, significant costs, and the risk of antibiotic resistance (27). The Canadian Pediatric Society guidelines (score 68.8) specify that bacterial infection in otherwise healthy children with bronchilitis is extremely rare, research on antibiotics is limited, and has failed to show benefit (28). They recommend that antibiotics should not be used except in cases in which there is clear evidence or strong suspicion of a secondary bacterial infection.

Antibiotics selected for EML for Bronchiolitis

Based on the RCT evidence and the CPGs, antibiotics are not recommened for bronchiolitis in otherwise healthy children unless there is clear evidence for or a strong suspicion of a secondary bacterial infection.

Reference List

1. World Health Organization. Essentail Medicines Selection. Comprehensive Review of Antibiotic Medicine. [Available from: https://www.who.int/selection_medicines/committees/expert/21/applications/comprehensive_antibiotics_rev/en/.
2. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.
3. Liu KX, Xu B, Wang J, Zhang J, Ding HB, Ariani F, et al. Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis. J Thorac Dis. 2014;6(3):221-9.
4. Chuchalin A, Zakharova M, Dokic D, Tokić M, Marschall HP, Petri T. Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis: a prospective, multicenter, observational study (AVANTI). BMC Pulm Med. 2013;13:5.
5. Siempos, II, Dimopoulos G, Korbila IP, Manta K, Falagas ME. Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. Eur Respir J. 2007;29(6):1127-37.
6. Dimopoulos G, Siempos, II, Korbila IP, Manta KG, Falagas ME. Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. Chest. 2007;132(2):447-55.
7. Korbila IP, Manta KG, Siempos, II, Dimopoulos G, Falagas ME. Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis: meta-analysis of randomized controlled trials. Canadian family physician Medecin de famille canadien. 2009;55(1):60-7.
8. Wang J, Xu H, Liu P, Li M. Network meta-analysis of success rate and safety in antibiotic treatments of bronchitis. Int J Chron Obstruct Pulmon Dis. 2017;12:2391-405.
9. Kelly C, Chalmers JD, Crossingham I, Relph N, Felix LM, Evans DJ, et al. Macrolide antibiotics for bronchiectasis. Cochrane Database Syst Rev. 2018;3(3):Cd012406.
10. Normansell R, Sayer B, Waterson S, Dennett EJ, Del Forno M, Dunleavy A. Antibiotics for exacerbations of asthma. Cochrane Database Syst Rev. 2018;6(6):Cd002741.
11. Wark P. Bronchitis (acute). BMJ clinical evidence. 2015;2015.
12. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database Syst Rev. 2017;6(6):Cd000245.
13. Linder JA, Sim I. Antibiotic treatment of acute bronchitis in smokers: a systematic review. J Gen Intern Med. 2002;17(3):230-4.
14. Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev. 2014(10):Cd005189.
15. Albert RH. Diagnosis and treatment of acute bronchitis. Am Fam Physician. 2010;82(11):1345-50.
16. Management of bronchitis in adults. Medstar Health. https://ct1.medstarhealth.org/content/uploads/sites/43/2016/08/Bronchitis-in-Adults-081516.pdf.
17. BMJ Best Practise – Bronchitis. https://bestpractice.bmj.com/topics/en-us/135.
18. Preventing and treating bronchitis. CDC. https://www.cdc.gov/antibiotic-use/community/downloads/Flyer-Bronchitis.pdf.

19. Medical Associates. Clinical practise guideline for treatment of acute bronchitis. file:///E:/Users/Mark/Downloads/Treatment_of_Acute_Bronchitis%20(7).pdf

20. Worrall G. Acute bronchitis. Can Fam Physician. 2008;54(2):238-9.
21. NICE. Cough (acute): antimicrobial prescribing. https://www.nice.org.uk/guidance/ng120. .
22. Harris AM, Hicks LA, Qaseem A. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164(6):425-34.
23. Onakpoya IJ, Hayward G, Heneghan CJ. Antibiotics for preventing lower respiratory tract infections in high-risk children aged 12 years and under. Cochrane Database Syst Rev. 2015(9):Cd011530.
24. Marchant JM, Petsky HL, Morris PS, Chang AB. Antibiotics for prolonged wet cough in children. Cochrane Database Syst Rev. 2018;7(7):Cd004822.
25. McCallum GB, Plumb EJ, Morris PS, Chang AB. Antibiotics for persistent cough or wheeze following acute bronchiolitis in children. Cochrane Database Syst Rev. 2017;8(8):Cd009834.
26. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2014;134(5):e1474-502.
27. Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr. 2014;40:65.
28. Friedman JN, Rieder MJ, Walton JM. Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health. 2014;19(9):485-98.
29. Diagnosis and management of bronchiolitis. Pediatrics. 2006;118(4):1774-93.