

References

1. Acuña-Izcaray A, Sánchez- Angarita E, Plaza V, Rodrigo G, Montes de Oca M, Gich I, et al. Quality assessment of asthma clinical practice guidelines: a systematic appraisal. *Chest*. 2013; 144(2): 390-7.
2. GEMA2009. Guía Española para el Manejo del Asma (GEMA 2009). *Arch Bronconeumol* 2009; 45(Supl 2):1-35 y GEMA 2009 (Spanish guideline on the management of asthma). *J Investig Allergol Clin Immunol*. Spain; 2010; 20(Suppl 1): 1-59. Disponible en www.gemasma.com (Última visita el 30 de marzo de 2015).
3. Grupo de trabajo sobre actualización de GPC. Actualización de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Instituto Aragonés de Ciencias de la Salud-I+CS; 2009. Guías de Práctica Clínica en el SNS: I+CS Nº 2007/02-01.
4. Grupo de trabajo sobre GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud-I+CS; 2007. Guías de Práctica Clínica en el SNS: I+CS Nº 2006/01.
5. BTS2012. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. 2007. <http://www.sign.ac.uk/guidelines> (Última visita el 30 de marzo de 2015).
6. GINA2014. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. 2006. <http://www.ginasthma.com> (Última visita el 30 de marzo de 2015).
7. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; 336(7650): 924-6.
8. Alonso-Coello P, Rigau D, Juliana Sanabria A, Plaza V, Miravittles M, Martínez L. Calidad y fuerza: el sistema GRADE para la formulación de recomendaciones en las guía de práctica clínica. *Arch Bronconeumol*. 2013; 49(6): 261-7.
9. ECRHHS 1996. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir*. 1996; 9: 687-95.
10. ECRHHS 2002. The European Community Respiratory Health Survey II. *Eur Respir J* 2002; 20: 1071-9.
11. Grupo Español del Estudio Europeo en Asma. Estudio europeo del asma Prevalencia de hiperreactividad bronquial y asma en jóvenes en 5 regiones de España. *Med Clin (Barc)*. 1996; 106: 761-7.
12. Urrutia I, Aguirre U, Sunyer J, Plana E, Muniozguren M, Martínez J, et al. Cambios en la prevalencia del asma en la población española del Estudio de Salud Respiratoria de la Comunidad Europea (ECRHS-II). *Arch Bronconeumol*. 2007; 43: 425-30.
13. Arnedo-Pena A, García-Marcos L, Carvajal I, Busquets-Monge R, Suarez-Varela I, Miner M, et al. Contaminación del aire y síntomas recientes de asma, rinitis alérgica y eczema atópico en escolares de 6 a 7 años. *Arch Bronconeumol*. 2009; 43: 224-9.
14. Carvajal-Urueña I, García- Marcos L, Busquets-Monge R, Morales Suárez-Varela M, García de Andoin N, Batlles-Garrido J, et al. Variaciones geográficas en la prevalencia de síntomas de asma en los niños y adolescentes españoles. *International Study on Asthma and Allergies in Childhood (ISAAC) fase III España*. *Arch Bronconeumol*. 2005; 41: 659-66.
15. García-Marcos L, Blanco A, García G, Guillén-Grima F, González C, Carvajal I, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain. *Allergy*. 2004; 59: 1301-7.
16. Pereira A, Sánchez JL, Maldonado JA, Sánchez I, Gil FL, García D. Incidencia de asma en 2 etapas de la vida: niños y adultos jóvenes de la ciudad de Huelva. *Arch Bronconeumol*. 2008; 44: 464-70.
17. Puig C, Fríguls B, Gómez M, García-Algar O, Sunyer J, Vall O. Relación entre las infecciones respiratorias de vías bajas durante el primer año de vida y el desarrollo de asma y sibilancias en niños. *Arch Bronconeumol*. 2010; 46: 514-21.
18. López-Silvarrey-Varela A, Pértega-Díaz S, Rueda-Esteban S, Sánchez-Lastres JM, San-José- González MA, Sampedro-Campos M, et al. Prevalencia de síntomas de asma en los niños y adolescentes de la Comunidad Autónoma de Galicia (España) y sus variaciones geográficas. *Arch Bronconeumol*. 2011; 47(6): 274-82.
19. Bercedo A, Redondo C, Lastra I, Gómez M, Mora E, Pacheco M, et al. Prevalencia de asma bronquial, rinitis alérgica y dermatitis atópica en adolescentes de 13-14 años de Cantabria. *Bol Pediatr*. 2004; 44: 9-19.
20. Arbes SJ Jr, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health

- and Nutrition Examination Survey. *J Allergy Clin Immunol.* 2007; 120: 1139-45.
21. Macsali F, Real FG, Plana E, Sunyer J, Anto J, Dratva J, et al. Early age at menarche, lung function, and adult asthma. *Am J Respir Crit Care Med.* 2011; 183: 8-14.
 22. Al-Sahab B, Hamadeh MJ, Ardern CI, Tamim H. Early menarche predicts incidence of asthma in early adulthood. *Am J Epidemiol.* 2011; 173: 64-70.
 23. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med.* 2002; 162: 1477-81.
 24. Carey VJ, Weiss ST, Tager IB, Leeder SR, Speizer FE. Airways responsiveness, wheeze onset, and recurrent asthma episodes in Young adolescents. The East Boston Childhood Respiratory Disease Cohort. *Am J Respir Crit Care Med.* 1996; 153: 356-61.
 25. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol.* 2002; 109: 419-25.
 26. Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol.* 2007; 120: 863-9.
 27. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and metaanalysis. January 28, 2014. *PLoS Med.* 2014; 11: e1001596.
 28. Ku MS, Sun HL, Sheu JN, Lee HS, Yang SF, Lue KH. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. *Pediatr Allergy Immunol.* 2012; 23: 623-8.
 29. Silvers KM, Frampton CM, Wickens K, Pattimore PK, Ingham T, Fishwick D, et al; New Zealand Asthma and Allergy Cohort Study Group. Breastfeeding protects against current asthma up to 6 years of age. *J Pediatr.* 2012; 160: 991-6.
 30. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr.* 2001; 139: 261-6.
 31. Tollånes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population based cohort study. *J Pediatr.* 2008; 153: 112-6.
 32. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ.* 1996; 312: 1195-9.
 33. Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol E, et al. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med.* 2006; 174: 1094-100.
 34. Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, et al. Risk factors for childhood asthma and wheezing. Importance of maternal and household smoking. *Am J Respir Crit Care Med.* 1996; 154: 681-8.
 35. Neuman A, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, et al.; ENRIECO Consortium. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med.* 2012; 186: 1037-43.
 36. Kerkhof M, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Aalberse RC, et al. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy.* 2009; 64: 1202-8.
 37. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, et al.; MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ.* 2001; 322: 390-5.
 38. Polosa R. An overview of chronic severe asthma. *Intern Med J.* 2008; 38: 190-8.
 39. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. *Chest.* 2006; 129: 610-8.
 40. Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJ. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. *Pediatr Allergy Immunol.* 2013; 24: 762-71.
 41. Levine SJ, Wenzel SE. Narrative review: the role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. *Ann Intern Med.* 2010; 152: 232-7.
 42. Barnes PJ. Pathophysiology of allergic inflammation. *Immunol Rev.* 2011; 242: 31-50.
 43. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol.* 2011; 128: 451-62.
 44. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med.* 2011; 364: 2006-15.
 45. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol.* 2010; 125: 1178-87.
 46. O'Byrne PM, Inman MD. Airway hyperresponsiveness. *Chest.* 2003; 123: 411S-6S.
 47. West AR, Syyong HT, Siddiqui S, Pascoe CD, Murphy TM, Maarsingh H, et al. Airway contractility and remodeling: links to asthma symptoms. *Pulm Pharmacol Ther.* 2013; 26: 3-12.
 48. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. *Nat Rev Immunol.* 2010; 10: 838-48.
 49. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med.* 2012; 18: 693-704.
 50. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol.* 2013; 13: 9-22.
 51. Maccowell AL, Peters SP. Neutrophils in asthma. *Curr Allergy Asthma Rep.* 2007; 7: 464-8.
 52. Lambrecht BN, Hammad H. The role of dendritic and epithelial cells as master regulators of allergic airway inflammation. *Lancet.* 2010; 376: 835-43.
 53. Yang M, Kumar RK, Hansbro PM, Foster PS. Emerging roles of pulmonary macrophages in driving the development of severe asthma. *J Leukoc Biol.* 2012; 91: 557-69.
 54. Lambrecht BN, Hammad H. The airway epithelium in asthma. *Nat Med.* 2012; 18: 684-92.
 55. Koziol-White CJ, Panettieri RA Jr. Airway smooth muscle and immunomodulation in acute exacerbations of airway disease. *Immunol Rev.* 2011; 242: 178-85.
 56. Holleman DR Jr, Simel DL. Does the clinical examination predict airflow limitation? *JAMA.* 1995; 274(4): 1051-7.
 57. BTS2004. British guideline on the management of asthma. A national clinic guideline. Revised edition April 2004. Edinburgh.
 58. Buke W, Fesinmeyer M, Reed K, Hampson L, Caristen C. Family history as a predictor of asthma risk. *AM J Prev Med.* 2003; 24(2): 160-9.

59. Bel EH. Clinical Phenotypes of Asthma. *Curr Opin Pulm Med*. 2004; 10: 44-50.
60. Martin P, Corral A, García E, Guillén M, Madueño A, Schwart P, et al. El asma en Atención Primaria. Guía de práctica clínica basada en la evidencia. Grupo de Respiratorio de la Sociedad Andaluza de Medicina Familiar y Comunitaria. Coord: Martín P. Granada: SAMFyC; 2001.
61. García C, Gómez-Pastrana D, Alcántara M, Andrés A, Aragón C, Bueno MG, et al. Proceso Asistencial Integrado Asma. Sevilla: Consejería de Salud de la Junta de Andalucía; 2012.
62. Wenzel SE. Asthma Phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012; 18: 716-25.
63. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using a clustering analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010; 181: 315-23.
64. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet*. 2008; 372: 1107-19.
65. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008; 32: 1096-110.
66. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev*. 2004; 5: 155-161.
67. Bousquet J, Gern JE, Martinez FD, Anto JM, Johnson CC, Holt PG, et al. Birth cohorts in asthma and allergic diseases: Report of a NIAID/NHLBI/ MeDALL joint workshop. *J Allergy Clin Immunol*. 2014; 133: 1535-46.
68. Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA, for the Childhood Asthma Management Program Research Group. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol*. 2014; 133: 1289-1300.
69. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvärinen A, Kaulek V, et al.; The PASTURE Study Group. Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med*. 2014; 189: 129-38.
70. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clin Exp Allergy*. 2010; 40: 1130-41.
71. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000; 162: 1403-6.
72. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol*. 2012; 130: 325-31.
73. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26: 948-68.
74. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest*. 2004; 126: 1875-82.
75. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. *Thorax*. 1992; 47: 162-6.
76. Phillips K, Osborne J, Lewis S, Harrison TW, Tattersfield AE. Time course of action of two inhaled corticosteroids, fluticasone propionate and budesonide. *Thorax*. 2004; 59: 26-30.
77. Reddel HK, Salome CM, Peat JK, Woolcock AJ. Which index of peak expiratory flow is most useful in the management of stable asthma? *Am J Respir Crit Care Med*. 1995; 151: 1320-5.
78. Boezen HM, Schouten JP, Postma DS, Rijcken B. Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20-70 yrs. *Eur Respir J*. 1994; 7: 1814-20.
79. Cockcroft DW. Bronchoprovocation methods: direct challenges. *Clin Rev Allergy Immunol*. 2003; 24: 19-26.
80. Van den Berge M, Meijer RJ, Kerstjens HA, de Reus DM, Koëter GH, Kauffman HF, et al. PC20 adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC20 methacholine. *Am J Respir Crit Care Med*. 2001; 163: 1546-50.
81. Anderson SD, Brannan J, Spring J, Spalding N, Rodwell LT, Chan K, et al. A new method for bronchial provocation testing in asthmatic subjects using a dry powder of mannitol. *Am J Respir Crit Care Med*. 1997; 156: 758-65.
82. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing—1999. *Am J Respir Crit Care Med*. 2000; 161: 309-29.
83. Perpiñá M, García F, Álvarez FJ, Cisneros C, Compte L, Entrenas LM, et al.; Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Guidelines for the study of nonspecific bronchial hyperresponsiveness in asthma. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). *Arch Bronconeumol*. 2013; 49(10): 432-46.
84. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. *J Allergy Clin Immunol*. 1992; 89: 23-30.
85. ATS/ERS2005. American Thoracic Society/European Respiratory Society. Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005; 171: 912-30.
86. Dweik R, Boggs P, Erzurum S, Irvin CJ, Leigh MW, Lundberg JO, et al. An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. *Am J Respir Crit Care Med*. 2011; 184: 602-15.
87. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest*. 2003; 123: 751-6.
88. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med*. 2004; 169: 473-8.
89. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax*. 2006; 61: 817-27.
90. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying Asthma Severity in Children: Mismatch Between Symptoms, Medication Use, and Lung Function. *Am J Respir Crit Care Med*. 2004; 15: 170(4): 426-32.

91. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011; 127: 382-9.
92. Lang AM, Konradsen J, Carlsen KH, Sachs-Olsen C, Mowinckel P, Hedlin G, et al. Identifying problematic severe asthma in the individual child-does lung function matter? *Acta Paediatr*. 2010; 99: 404-10.
93. Van Dalen C, Harding E, Parkin J, Cheng S, Pearce N, Douwes J. Suitability of forced expiratory volume in 1 s/forced vital capacity vs. percentage of predicted forced expiratory volumen in 1 s for the classification of asthma severity in adolescents. *Arch Pediatr Adolesc Med*. 2008; 162: 1169-74.
94. Galant SP, Morphew T, Amaro S, Liao O. Value of the broncodilator response in assessing controller naïve asthmatic children. *J Pediatr*. 2007; 151: 457-62.
95. Tse AM, Gold DR, Sordillo JE, Hoffman EB, Gillman MW, Rifas-Shiman SL, et al. Diagnostic accuracy of the broncodilator response in children. *A Allergy Clin Immunol*. 2013; 132: 554-9.
96. Müller-Brandes G, Krämer U, Gappa M, Seitner-Sorge G, Hüls A, von Berg A, et al. LUNOKID: can numerical American Thoracic Society/European Respiratory Society quality criteria replace visual inspection of spirometry? *Eur Respir J*. 2014; 43: 1347-56.
97. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A. 'ATS/ERS TASK force: standardisation of lung function testing'. Standardisation of spirometry. *Eur Respir J*. 2005; 26: 319-38.
98. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF 25-75% and FEF 75% does not contribute to clinical decision making. *Eur Respir J*. 2014; 43: 1051-58.
99. Asensio O, Cerdón A, Elorz J, Moreno A, Villa JR; Grupo de Técnicas de la Sociedad Española de Neumología Pediátrica. Estudio de la función pulmonar en el paciente colaborador. Parte II. *An Pediatr (Barc)*. 2007; 66(5): 518-30.
100. Pérez-Yarza EG, Villa JR, Cobos N, Navarro M, Salcedo A, Martín C, et al. Espirometría forzada en preescolares sanos bajo las recomendaciones de la ATS/ERS: estudio CANDELA. *An Pediatr (Barc)*. 2009b; 70(1): 3-11.
101. Stanojevic S, Wade A, Lum S, Stocks J. Reference equations for pulmonary function tests in preschool children: A review. *Pediatric Pulmonology*. 2007; 42(10): 962-72.
102. Beydon N, Davis SD, Lombardi E, Allen JL, Arets H, Aurora P, et al.; on behalf of the American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children. *Am J Respir Crit Care Med*. 2007; 175: 1304-45.
103. Borrego LM, Stocks J, Almeida I, Stanojevic S, Antunes J, Leiria-Pinto P, et al. Broncodilator responsiveness using spirometry in healthy and asthmatic preschool children. *Arch Dis Child*. 2013; 98: 112-7.
104. Cobos N, Pérez-Yarza EG, Sardón O, Reverté C, Gartner S, Korta J. Óxido nítrico exhalado en niños: un indicador no invasivo de la inflamación de las vías aéreas. *Arch Bronconeumol*. 2008; 44(1): 41-51.
105. Caudri D, Wijga AH, Hoekstra M, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax*. 2010; 65: 801-7.
106. See KC, Christiani DC. Normal values and thresholds for the clinical interpretation of exhaled nitric oxide levels in the US general population. *Chest*. 2013; 143: 107-16.
107. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al.; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011; 184: 602-15.
108. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. *Eur Respir J*. 2008; 31: 539-46.
109. Smith AD, Covan JO, Brasslet KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med*. 2005; 172: 453-9.
110. Pijnenburg MW, Hofhuis W, Hop WC, De Jonste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax*. 2005; 60: 215-8.
111. Van der Heijden HH, Brouwer ML, Hoekstra F, van der Pol P, Merkus PJ. Reference values of exhaled nitric oxide in healthy children 1-5 years using off-line tidal breathing. *Pediatr Pulmonol*. 2014; 49: 291-5.
112. Burbach GJ, Heinzerling LM, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy*. 2009; 64: 1507-15.
113. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al.; Global Allergy and Asthma European Network; Allergic Rhinitis and its Impact on Asthma. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy*. 2012; 67: 18-24.
114. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al.; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008; 100(3 Suppl 3): S1-148.
115. De Vos G, Nazari R, Ferastraoraru D, Parikh P, Geliebter R, et al. Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years. *Ann Allergy Asthma Immunol*. 2013; 110: 438-43.
116. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE, et al. A WAO - ARIA - GA2LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J*. 2013; 6(1): 17.
117. Sastre J, Landivar ME, Ruiz-García M, Andregnette-Rosigno MV, Mahillo I. How molecular diagnosis can change allergen-specific immunotherapy prescription in a complex pollen area. *Allergy*. 2012; 67: 709-11.
118. Vandenas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al.; the ERS Task Force on Specific Inhalation Challenges with Occupational Agents. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. *Eur Respir J*. 2014; 43(6): 1573-87.

119. NAEPP-EP32007. Nacional Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute, 2007.
120. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol.* 2006; 117: 563-70.
121. Stoloff SW, Boushey HA. Severity, control, and responsiveness in asthma. *J Allergy Clin Immunol.* 2006; 117: 544-8.
122. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J.* 2008; 32: 545-54.
123. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol.* 1996; 98: 1016-8.
124. Osborne ML, Vollmer WM, Pedula KL, Wilkins J, Buist AS, O'Hollaren M. Lack of correlation of symptoms with specialist-assessed long-term asthma severity. *Chest.* 1999; 115: 85-91.
125. GINA2006. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. 2006. <http://www.ginasthma.com> (Última visita el 30 de marzo de 20015).
126. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al.; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med.* 2004; 170: 836-44.
127. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control test. *J Allergy Clin Immunol.* 2004; 113: 59-65.
128. Vega JM, Badia X, Badiola C, López-Viña A, Olaguíbel JM, Picado C, et al.; Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Test (ACT). *J Asthma.* 2007; 44: 867-72.
129. Olaguíbel J, Vega J, Sastre J, Picado C, López A, Badia X, et al. Validation of the Spanish version of the "Asthma Control Questionnaire" (ACQ). *Allergy.* 2006; 61(Suppl 2): 124.
130. Schatz M, Kosinski M, Yaras AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol.* 2009a; 124: 719-23.
131. Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006; 100: 616-21.
132. Olaguíbel JM, Quirce S, Julia B, Fernandez C, Fortuna AM, Molina J, et al. Measurement of asthma control according to global initiative for asthma guidelines: a comparison with the asthma control questionnaire. *Respir Res.* 2012; 13: 50.
133. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: Systematic review and meta-analysis. *J Allergy Clin Immunol.* 2013; 131: 695-703.
134. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J.* 2004; 23(2): 287-91.
135. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res.* 1996; 5(1): 35-46.
136. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J.* 1999a; 14(1): 32-8.
137. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest.* 2004; 126: 1875-82.
138. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. *Chest.* 2007; 132: 1151-61.
139. Kohansal R, Martinez-Cambor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med.* 2009; 180: 3-10.
140. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW; START Investigators Group. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med.* 2009; 179: 19-24.
141. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med.* 1998; 339: 1194-200.
142. Baur X, Aasen TB, Burge PS, Heederik D, Henneberger PK, Maestrelli P, et al; ERS Task Force on the Management of Work-related Asthma. The management of work-related asthma guidelines: a broader perspective. *Eur Respir. Rev.* 2012; 21: 125-39.
143. Ulrik CS. Eosinophils and pulmonary function: an epidemiologic study of adolescents and young adults. *Ann Allergy Asthma Immunol.* 1998; 80: 487-93.
144. Petsky HL1, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax.* 2012; 67: 199-208.
145. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet.* 2008; 372(9643): 1065-72.
146. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012; 380(9842): 651-9.
147. Belda J, Giner J, Casan P, Sanchis J. Mild exacerbations and eosinophilic inflammation in patients with stable, well-controlled asthma after 1 year of follow-up. *Chest.* 2001; 119: 1011-7.
148. Castillo JA, de Benito J, Escribano A, Fernández M, García de la Rubia S, Garde J, et al. Consenso sobre tratamiento del asma en pediatría. *An Pediatr (Barc).* 2007; 67(3): 253-73.
149. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. on behalf of the American Thoracic Society/ European Respiratory Society Task Force on Asthma Control and Exacerbations. An Official American Thoracic Society/ European Respiratory Society Statement: Asthma Control and Exacerbations. Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am J Respir Crit Care Med.* 2009; 180: 59-99.

150. Pérez-Yarza EG, Badía X, Badiola C, Cobos N, Garde J, Ibero M, et al.; on behalf of the CAN Investigator Group. Development and validation of a questionnaire to assess asthma control in pediatrics. *Pediatr Pulmonol*. 2009a; 44: 54-63.
151. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol*. 2007; 119(4): 817-25.
152. Rodríguez-Martínez CE, Melo-Rojas A, Restrepo-Gualteros SM, Sossa-Briceño MP, Nino G. Validation of the Spanish version of the childhood asthma control test (cACT) in a population of Hispanic children. *J Asthma*. 2014; 51(8): 855-62.
153. Pérez-Yarza EG, Castro JA, Villa JR, Garde J, Hidalgo J; on behalf of the VESCAI Group. Validation of a Spanish version of the Childhood Asthma Control Test (Sc-ACT) for use in Spain. 2015 (pendiente de publicación).
154. ICON. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gem J, Lemanske R, et al. International consensus on pediatric asthma. *Allergy*. 2012; 67: 976-97.
155. Boulet LP, Becker A, Berubé D, Beveridge R, Ernst P, on behalf of the Canadian Asthma Consensus Group. Summary of recommendations from the Canadian Asthma Consensus report 1999. *CMAJ*. 1999; 161(11 Supl): S1-S12.
156. Gibson PG, Powell H, Ducharme FM. Differential effects of maintenance long-acting beta-agonist and inhaled corticosteroid on asthma control and asthma exacerbations. *J Allergy Clin Immunol*. 2007; 119: 344-50.
157. Blakey JD, Woolnough K, Fellows J, Walker S, Thomas M, Pavord ID. Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. *Prim Care Respir J*. 2013; 22: 344-52.
158. Cockcroft DW. As-needed inhaled beta2-adrenoceptor agonists in moderate-to-severe asthma: current recommendations. *Treat Respir Med*. 2005; 4: 169-74.
159. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003; 361(9363): 1071-6.
160. Zeiger RS, Baker JW, Kaplan MS, Pearlman DS, Schatz M, Bird S, et al. Variability of symptoms in mild persistent asthma: baseline data from the MIAMI study. *Respir Med*. 2004; 98: 898-905.
161. Tan RA, Spector SL. Exercise-induced asthma: diagnosis and management. *Ann Allergy Asthma Immunol*. 2002; 89: 226-35.
162. Adams NP, Bestall JC, Lasserson TJ, Jones PW, Cates C. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2005; (4): CD003135.
163. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005(1): CD002738.
164. Koh MS, Irving LB. Evidence-based pharmacologic treatment for mild asthma. *Int J Clin Pract*. 2007; 61: 1375-9.
165. Reddel HK, Belousova EG, Marks GB, Jenkins CR. Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomised controlled trial. *Prim Care Respir J*. 2008; 17: 39-45.
166. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med*. 2001; 164(8 Pt 1): 1392-7.
167. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol*. 2001; 107: 937-44.
168. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med*. 2005; 352: 1519-28.
169. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med*. 2005; 118: 649-57.
170. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2012; (5): CD002314.
171. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. ALA. American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med*. 2007; 356: 2027-39.
172. Busse WW, Casale TB, Dykewicz MS, Meltzer EO, Bird SR, Hustad CM, et al. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. *Ann Allergy Asthma Immunol*. 2006; 96: 60-8.
173. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. 2006; 61: 737-42.
174. Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. *Cochrane Database Syst Rev*. 2009; (4): CD005307.
175. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. *Respir Med*. 2002; 96: 432-8.
176. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet*. 1994; 343(8904): 1006-8.
177. Dudley T, Parker S, Baldwin R. Clinical inquiries. Is nedocromil effective in preventing asthmatic attacks in patients with asthma? *J Fam Pract*. 2004; 53: 927-8.
178. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med*. 1996; 153: 1481-8.
179. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med*. 1997; 337: 1405-11.
180. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ*. 2000; 320: 1368-73.

181. Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev.* 2005; (4): CD005533.
182. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax.* 2005; 60: 730-4.
183. Barnes PJ, Nicolini G, Bizzi A, Spinola M, Singh D. Do inhaled corticosteroid/long-acting beta2-agonist fixed combinations provide superior clinical benefits compared with separate inhalers? A literature reappraisal. *Allergy Asthma Proc.* 2012; 33: 140-4.
184. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budsonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med.* 2005; 171: 129-36.
185. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Laloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet.* 2006; 368(9537): 744-53.
186. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest.* 2006; 129: 246-56.
187. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J.* 2005; 26: 819-28.
188. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez Aguilar NE, et al. Budesonide/ formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med.* 2007; 101: 2437-46.
189. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martínez-Jimenez NE, et al. Effect of budesonide/ formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.* 2007; 61: 725-36.
190. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2013; 12: CD009019.
191. Papi A, Corradi M, Pigeon Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med.* 2013; 1: 23-31.
192. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol.* 2002; 109: 410-8.
193. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Aust.* 2003; 178: 223-5.
194. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev.* 2010: CD005533.
195. Pieters WR, Wilson KK, Smith HC, Tamminga JJ, Sondhi S. Salmeterol/fluticasone propionate versus fluticasone propionate plus montelukast: a cost-effective comparison for asthma. *Treat Respir Med.* 2005; 4: 129-38.
196. Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. *Thorax.* 2008; 63: 453-62.
197. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev.* 2006; (4): CD003137.
198. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus antileukotrienes for chronic asthma. *Cochrane Database of Systematic Reviews.* 2014; (1): CD003137.
199. Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database Syst Rev.* 2005; (4): CD005535.
200. Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res.* 2011; 12: 38.
201. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol.* 1982; 70: 288-98.
202. Tonelli M, Zingoni M, Bacci E, Dente FL, Di Franco A, Giannini D, et al. Short-term effect of the addition of leukotriene receptor antagonists to the current therapy in severe asthmatics. *Pulm Pharmacol Ther.* 2003; 16: 237-40.
203. Virchow JC Jr, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med.* 2000; 162(2 Pt 1): 578-85.
204. Inoue H, Komori M, Matsumoto T, Fukuyama S, Matsumura M, Nakano T, et al. Effects of salmeterol in patients with persistent asthma receiving inhaled corticosteroid plus theophylline. *Respiration.* 2007; 74: 611-6.
205. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med.* 2012; 367: 1198-207.
206. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. *J Asthma Allergy.* 2014; 7: 11-21.
207. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005; 60: 309-16.
208. Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma. *Allergy.* 2008; 63: 592-6.
209. Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. *Curr Med Res Opin.* 2007; 23: 2379-86.

210. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane database of systematic reviews*. 2014; (1): CD003559.
211. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. 2013; 68: 322-9.
212. Wong EH, Porter JD, Edwards MR, Johnston SL. The role of macrolides in asthma: current evidence and future directions. *Lancet Respir Med*. 2014; 2(8): 657-70.
213. Mash B, Bheekie A, Jones PW. Inhaled vs oral steroids for adults with chronic asthma. *Cochrane Database Syst Rev*. 2000; (2): CD002160.
214. Polosa R, Knoke JD, Russo C, Piccillo G, Caponnetto P, Sarva M, et al. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol*. 2008; 121: 1428-34.
215. Newman SP, Clarke SW. Therapeutic aerosols 1--physical and practical considerations. *Thorax*. 1983; 38: 881-6.
216. Clarke SW, Newman SP. Therapeutic aerosols 2--Drugs available by the inhaled route. *Thorax*. 1984; 39: 1-7.
217. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al.; International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011; 37: 1308-31.
218. Consenso SEPAR-ALAT sobre terapia inhalada. *Arch Bronconeumol*. 2013; 49(Supl.1): 1-14.
219. Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, et al. Inhaler Error Steering Committee. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. *Respir Med*. 2013; 107: 37-46.
220. Sanchis J, Corrigan C, Levy ML, Viejo JL; ADMIT Group. Inhaler devices - from theory to practice. *Respir Med*. 2013; 107: 495-502.
221. Brown PH, Greening AP, Crompton GK. Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax*. 1993; 48: 233-8.
222. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. *J Aerosol Med*. 1996; 9: 55-70.
223. Newman SP. Spacer devices for metered dose inhalers. *Clin Pharmacokinet*. 2004; 43: 349-60.
224. Hess DR. Aerosol delivery devices in the treatment of asthma. *Respir Care*. 2008; 53: 699-723.
225. Plaza V, Sanchis J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. CESEA Group. *Respiration*. 1998; 65: 195-8.
226. Giner J, Torrejón M, Ramos A, Casan P, Granel C, Plaza V, et al. Patient preference in the choice of dry powder inhalers. *Arch Bronconeumol*. 2004; 40: 106-9.
227. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med*. 2007; 175: 783-90.
228. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med*. 2005; 171: 109-14.
229. Clearie KL, McKinlay L, Williamson PA, Lipworth BJ. Fluticasone/ Salmeterol combination confers benefits in people with asthma who smoke. *Chest*. 2012; 141: 330-8.
230. Hedman L, Bjerg A, Sundberg S, Forsberg B, Rönmark E. Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. *Thorax*. 2011; 66: 20-5.
231. Jiménez CA, Barrueco M, Solano S, Torrecilla M, Domínguez M, Díaz- Maroto JL, et al. Recomendaciones en el abordaje diagnóstico y terapéutico del tabaquismo. Documento de consenso. *Arch Bronconeumol*. 2003; 39: 35-41.
232. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995; 332: 133-8.
233. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. *N Engl J Med*. 2010; 363: 1139-45.
234. Sims M, Maxwell R, Gilmore A. Short-term impact of the smokefree legislation in England on emergency hospital admissions for asthma among adults: a population-based study. *Thorax*. 2013; 68: 619-24.
235. Plaza V, Serrano J, Picado C, Sanchis J; High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur Respir J*. 2002; 19: 846-52.
236. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczyńska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy*. 2007; 62: 1111-8.
237. Casadevall J, Ventura PJ, Mullol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax*. 2000; 55: 921-4.
238. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 2004; 351: 1068-80.
239. Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Ann Allergy Asthma Immunol*. 2004; 92: 420-5.
240. Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest*. 2005; 127: 1565-71.
241. Orriols R, Abu K, Alday E, Cruz MJ, Gáldiz JB, Isidro I, et al. *Arch Bronconeumol*. 2006; 42: 457-74.
242. Portnoy J, Chew GL, Phipatanakul W, Williams PB, Grimes C, Kennedy K, et al. Environmental assessment and exposure reduction of cockroaches: a practice parameter. *J Allergy Clin Immunol*. 2013; 132: 802-8.
243. Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. *Clin Exp Allergy*. 2003; 33: 1648-53.
244. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med*. 2003; 349: 225-36.

245. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy*. 2008; 63: 646-59.
246. Htut T, Higenbottam TW, Gill GW, Darwin R, Anderson PB, Syed N. Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial. *J Allergy Clin Immunol*. 2001; 107: 55-60.
247. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol*. 2003; 111: 169-76.
248. Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. *Cochrane Database of Systematic Reviews*. 2007; (1): CD001563.
249. Portnoy J, Miller JD, Williams PB, Chew GL, Miller JD, Zaitoun F, et al.; Joint Taskforce on Practice Parameters; Practice Parameter Workgroup. Environmental assessment and exposure control of dust mites: a practice parameter. *Ann Allergy Asthma Immunol*. 2013; 111: 465-507.
250. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003; (4): CD001186.
251. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database of Systematic Reviews*. 2010; (8): CD001186.
252. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med*. 1997; 336: 324-31.
253. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol*. 2004; 113: 1129-36.
254. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Álvarez Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *ClinExp Allergy*. 2004; 34: 527-31.
255. Olaguibel JM, Álvarez MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Investig Allergol Clin Immunol*. 2005; 15: 9-16.
256. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy*. 2008; 63(10): 1280-91.
257. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: A systematic review. *JAMA*. 2013; 309: 1278-88.
258. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. 1999; 341: 468-75.
259. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al.; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007; 62: 943-8.
260. Pajno GB, Barberio G, de Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *ClinExp Allergy*. 2001; 31: 1392-7.
261. Nasser S, Vestenbæk U, Beriot-Mathiot A, Poulsen P. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy*. 2008; 63: 1624-9.
262. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. *J Allergy Clin Immunol*. 2013; 131: 1084-91.
263. Abadoglu O, Mungan D, Pasaoglu G, Celik G, Misirligil Z. Influenza vaccination in patients with asthma: effect on the frequency of upper respiratory tract infections and exacerbations. *J Asthma*. 2004; 41: 279-83.
264. Christy C, Aligne CA, Auinger P, Pulcino T, Weitzman M. Effectiveness of influenza vaccine for the prevention of asthma exacerbations. *Arch Dis Child*. 2004; 89: 734-5.
265. Sheikh A, Alves A, Dhami S. Pneumococcal vaccine for asthma. *Cochrane Database Syst. Rev*. 2002; (1): CD002165.
266. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Eng J Med*. 2000; 342: 232-9.
267. Jain VK, Rivera L, Zaman K, Espos RA Jr, Sirivichayakul C, Quiambao BP, et al. Vaccine for Prevention of Mild and Moderate-to- Severe Influenza in Children. *N Eng J Med*. 2013; 369: 2481-91.
268. Johnston NW, Sears MR. Asthma exacerbations. *Epidemiology Thorax*. 2006; 61: 722-8.
269. Hughes DM, McLeod M, Garner B, Goldbloom RB. Controlled trial of a home and ambulatory program for asthmatic children. *Pediatrics*. 1991; 87: 54-61.
270. Colland VT. Learning to cope with asthma: a behavioural self-management program for children. *Patient Educ Couns*. 1993; 22: 141-52.
271. Van der Palen J, Klein JJ, Zielhuis GA, van Herwaarden CL, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. *Patient Educ Couns*. 2001; 43: 161-9.
272. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood Bauman A, et al. Educación para el autocuidado y examen médico regular para adultos con asma (Revisión Cochrane traducida). En: *La Biblioteca Cochrane Plus*, 2008 Número 1. Oxford: Update Software Ltd. Disponible en: <http://www.update-software.com> (Última visita el 30 de marzo de 2015).
273. Powell H, Gibson PG. Opciones para la educación sobre el autocuidado para los adultos con asma (Revisión Cochrane traducida). En: *La Biblioteca Cochrane Plus*, 2008 Número 1. Oxford: Update Software Ltd. Disponible en: <http://www.update-software.com> (Última visita el 30 de marzo de 2015).
274. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax*. 2014; 69(Suppl 1): 1-192.
275. Partridge MR. Patient education. En: O'Byrne P, Thomsen NC, eds. *Manual of asthma management*. WB Saunders; 1995: 378-92.
276. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003; (1): CD001117.

277. Gibson PG, Powell H, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, et al. Limited (informationonly) patient education programs for adults with asthma. *Cochrane Database Syst Rev.* 2002; (2): CD001005.
278. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al.; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med.* 2011; 105: 930-8. Erratum in: *Respir Med.* 2012; 106: 757. Del Donno, Mario [corrected to Del Donno, Mario].
279. Haynes RB1, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev.* 2002; (2): CD000011.
280. Creer TL. Medication compliance and childhood asthma. En: Krasnegor NA, Epstein L, Johnson SB, Yaffe SJ, editors. *Developmental aspects of health compliance behavior.* Hittsdale, NS: Lawrence Associate; 1993. pp. 303-33.
281. Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, et al.; Victorian Asthma Mortality Study Group. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med.* 2001; 163: 12-8.
282. Douglass J, Aroni R, Goeman D, Stewart K, Sawyer S, Thien F, et al. A qualitative study of action plans for asthma. *BMJ.* 2002; 324: 1003-5.
283. Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? *Thorax.* 2004; 59: 922-4.
284. Lahdensuo A. Guided self management of asthma-how to do it. *BMJ.* 1999; 319: 759-60.
285. Côté J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. *Am J Respir Crit Care Med.* 2001; 163: 1415-9.
286. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax.* 2004; 59: 94-9.
287. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. *Thorax.* 1995; 50(12): 1274-9.
288. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. *J Asthma.* 2010; 47(2): 162-5.
289. Horn CR, Clark TJ, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. *Respir Med.* 1990; 84(1): 67-70.
290. Jentzsch NS, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med.* 2012; 106(3): 338-43.
291. Hyland M. Types of noncompliance. *Eur Respir Rev.* 1998; 8: 255-9.
292. Rand CS. Adherence to asthma therapy in the preschool child. *Allergy.* 2002; 57s: 48-57.
293. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986; 24(1): 67-74.
294. Val A, Amorós G, Martínez P, Fernández ML, León M. Descriptive study of patient compliance in pharmacologic antihypertensive treatment and validation of the Morisky and Green test. *Aten Primaria.* 1992; 10(5): 767-70.
295. Cohen JL, Mann DM, Wisnivesky JP, Horne R, Leventhal H, Musumeci Szabó TJ, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy, Asthma Immunol.* 2009; 103(4): 325-31.
296. Plaza V, Fernández-Rodríguez C, Melero C, Cosío BG, Entrenas LM, López-Viña A, Perez de Llano L, Gutierrez-Pereyra F, Tarragona E y Palomino R. Validation of the 'Test of the Adherence to Inhalers' (TAI) for asthma and COPD patients. *J Aerosol Med Pulm Drug Deliver* 2015 (en prensa).
297. Urrutia I, Plaza V, Pascual S, Cisneros C, Entrenas LM, Luengo MT, et al. Asthma control and concordance of opinions between patients and pulmonologists. *J Asthma.* 2013; 50(8): 877-83.
298. Van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J; SMASHING (Self-Management in Asthma Supported by Hospitals, ICT, Nurses and General Practitioners) Study Group. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. *Ann Intern Med.* 2009; 151: 110-20.
299. Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med.* 2003; 168: 1095-9.
300. Borgmeyer A, Gyr PM, Jamerson PA, Henry LD. Evaluation of the role of the pediatric nurse practitioner in an inpatient asthma program. *J Pediatr Health Care.* 2008; 22: 273-81.
301. Armour CL, Reddel HK, LeMay KS, Saini B, Smith LD, Bosnic Anticevich SZ, et al. Feasibility and effectiveness of an evidence-based asthma service in Australian community pharmacies: a pragmatic cluster randomized trial. *J Asthma.* 2013; 50: 302-9.
302. Kueth MC, Vaessen-Verberne AA, Elbers RG, Van Aalderen WM. Nurse versus physician-led care for the management of asthma. *Cochrane Database Syst Rev.* 2013; 2: CD009296.
303. Cano G, Dastis C, Morales I, Manzanares ML, Fernández A, Martín L. Ensayo clínico aleatorio para evaluar la eficacia de una intervención educativa desarrollada en atención primaria sobre asmáticos adultos. *Aten Primaria.* 2014; 46: 117-39.
304. Woodruff PG, Emond SD, Singh AK, Camargo CA Jr. Sudden-onset severe acute asthma: clinical features and response to therapy. *Acad Emerg Med.* 1998; 5: 695-701.
305. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma: a case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med.* 1998; 157: 1804-9.
306. Mitchell I, Tough SC, Semple LK, Green FH, Hessel PA. Near-fatal asthma: a population-based study of risk factors. *Chest.* 2002; 121: 1407-13.
307. Serrano J, Plaza V, Sureda B, de Pablo J, Picado C, Bardagi S, et al. Alexithymia: a relevant psychological variable in near-fatal asthma. *Eur Respir J.* 2006; 28: 296-302.
308. Rodrigo GJ, Plaza V, Bardagi S, Castro-Rodríguez JA, de Diego A, Liñán S, et al. Guía ALERTA 2. América Latina y España: Recomendaciones para la prevención y el Tratamiento de la exacerbación Asmática. *Arch Bronconeumol.* 2010; 46: s2-s20.
309. McFadden ER, Kisser R, De Groot WJ. Acute bronchial Asthma: relations between clinical and physiological manifestations. *Engl J Med.* 1973; 288: 221-5.
310. Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma patients in the emergency department. *Chest.* 1998; 114: 1016-21.

311. Carruthers DM, Harrison BD. Arterial Blood gas analysis or oxygen saturation in the assessment of acute asthma? *Thorax*. 1995; 50: 186-8.
312. Rodrigo GJ, Rodrigo C, Hall JB. Acute Asthma in adults. A review. *Chest*. 2004; 125: 1081-02.
313. Honkoop PJ, Taylor DR, Smith AD, Snoeck-Stroband JB, Sont JK. Early detection of asthma exacerbations by using action points in self-management plans. *Eur Respir J*. 2013; 41: 53-9.
314. Reisner C, Kotch A, Dworkin G. Continuous versus frequent intermittent nebulization of albuterol in acute asthma: a randomized, prospective study. *Ann Allergy Asthma Immunol*. 1995; 75: 41-7.
315. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database of Systematic Reviews*. 2006; (2): CD000052.
316. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database of Systematic Reviews*. 2001; (1): CD002178.
317. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev*. 2000; (2): CD001740.
318. Rowe BH, Spooner CH, Ducharme FM, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database of Systematic Reviews*. 2007; (3): CD000195.
319. Hasegawa T, Ishihara K, Takakura S, Fujii H, Nishimura T, Okazaki M, et al. Duration of systemic corticosteroids in the treatment exacerbation; a randomized study. *Intern Med*. 2000; 39: 794-7.
320. Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, et al. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. *Thorax*. 2002; 57: 869-74.
321. Tapp S, Lasserson TJ, Rowe BH. Education interventions for adults who attend the emergency room for acute asthma. *Cochrane Database of Systematic Reviews*. 2007; (3): CD003000.
322. Rodrigo GJ, Rodriguez-Verde M, Peregalli V, Rodrigo C. Effects of short-term 28% and 100% oxygen in pCO₂ and peak expiratory flow rate in acute Asthma. A randomized trial. *Chest*. 2003; 124: 1312-7.
323. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database of Systematic Reviews*. 2013; (9): CD000052.
324. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. *Chest*. 2002; 122: 160-5.
325. Camargo CA, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. *Cochrane Database of Systematic Reviews* 2003; (4): CD001115.
326. Travers AH, Milan SJ, Jones AP, Camargo Jr CA, Rowe BH. Addition of intravenous beta₂-agonists to inhaled beta₂-agonists for acute asthma. *Cochrane Database of Systematic Reviews*. 2012; (12): CD010179.
327. Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and beta₂ agonists for the treatment of acute asthma. A meta-analysis of randomized trials. *Am J Emerg Med*. 2006b; 24: 217-22.
328. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; 60: 740-6.
329. Manser R, Reid D, Abramson MJ. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database of Systematic Reviews*. 2001; (1): CD001740.
330. Edmonds ML, Milan SJ, Camargo CA Jr, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev*. 2012; 12: CD002308.
331. Alangari AA. Corticosteroids in the treatment of acute asthma. *Ann of Thorac Med*. 2014; 9(4): 187-92.
332. Ratto D, Alfaro C, Sipsey J, Glosky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988; 260: 527-9.
333. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet*. 1986; 1(8474): 181-4.
334. Lederle FA, Pluhar RE, Joseph AM, Niewoehner DE. Tapering of corticosteroid therapy following exacerbation of asthma. A randomized, double-blind, placebo-controlled trial. *Arch Intern Med*. 1987; 147: 2201-3.
335. Hatton MQ, Vathenen AS, Allen MJ, Davies S, Cooke NJ. A comparison of "abruptly stopping" with "tailing off" oral corticosteroids in acute asthma. *Respir Med*. 1995; 89: 101-4.
336. Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta₂-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews*. 2012; (12): CD002742.
337. Rowe BH, Bretzlaff J, Bourdon C, Bota G, Blitz S, Camargo CA. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database of Systematic Reviews*. 2000; (1): CD001490.
338. FitzGerald JM. Magnesium sulfate is effective for severe acute asthma treated in the emergency department. *West J Med*. 2000; 172(2): 96.
339. Gallegos-Solórzano MC, Pérez Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjunct management of severe asthma crisis in an emergency department. *Pulm Pharmacol Ther*. 2010; 23: 432-7.
340. Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database of Systematic Reviews*. 2012; (12): CD003898.
341. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients. *Cochrane Database of Systematic Reviews*. 2006; (4): CD002884.
342. Colebourn CL, Barber V, Young JD. Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia*. 2007; 62: 34-42.
343. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven β₂-agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014; 112(1): 29-34.

344. Pallin M, Naughton MT. Noninvasive ventilation in acute asthma. *J Crit Care*. 2014; 29: 586-93.
345. Wilson MM, Irwin RS, Connolly AE, Linden C, Manno MM. A prospective evaluation of the 1-hour decision point for admission versus discharge in acute asthma. *J Intensive Care Med*. 2003; 18: 275-85.
346. Kelly AM, Kerr D, Powell C. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med*. 2004; 98: 777-81.
347. Grunfeld A, Fitzgerald JM. Discharge considerations in acute asthma. *Can Respir J*. 1996; 3: 322-4.
348. Schatz M, Rachelefsky G, Krishnan JA. Follow-up after acute asthma episodes: what improves future outcomes? *Proc Am Thorac Soc*. 2009b; 6: 386-93.
349. Pearson MG, Ryland I, Harrison BD. National audit of acute severe asthma in adults admitted to hospital. Standards of Care Committee, British Thoracic Society. *Qual Health Care*. 1995; 4: 24-30.
350. Castro-Rodriguez JA, Pedersen S. The role of inhaled corticosteroids in management of asthma in infants and preschoolers. *Curr Opin Pulm Med*. 2013; 19: 54-9.
351. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N. Engl. J Med*. 2006; 354: 1985-97.
352. Teper AM, Kofman CD, Szulman GA, Vidaurreta SM, Maffey AF. Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. *Am. J Respir Crit Care Med*. 2005; 171: 587-90.
353. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev*. 2000; 1: CD001107.
354. Brand P, Caudri D, Eber E, Gaillard EA, García-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J*. 2014; 43: 1172-77.
355. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med*. 2006; 354: 1998-2005.
356. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus induced wheezing in young children. *N Engl J Med*. 2009; 360: 339-53.
357. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr, et al; CARE Network of the National Heart, Lung, and Blood Institute. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med*. 2011; 365(21): 1990-2001.
358. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. CAMP Research Group. Effect of Inhaled Glucocorticoids in Childhood on Adult Height. *N Engl J Med*. 2012; 367 (10): 904-12.
359. Ozkaya E, Çakir E, Uzuner S, Erenberk U, Dundaröz MR. Bone mineral density and associated parameters in pre-pubertal children with asthma treated with long-term fluticasone propionate. *Allergol Immunopathol*. 2013; 41(2): 102-7.
360. Szeffler SJ, Phillips BR, Martínez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005; 115: 233-42.
361. Price D, Musgrave SD, Shepstone L, Hillyer EV, Sims EJ, Gilbert RF, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med*. 2011; 364(18): 1695-707.
362. Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. *Eur Respir J*. 2005; 25: 289-94.
363. Ducharme FM. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: systematic review of current evidence. *BMJ*. 2002; 324: 1545.
364. Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr*. 2001; 138: 694-8.
365. Bisgaard H, Zielen S, García ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med*. 2005; 171: 315-22.
366. Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatment on exercise-induced bronchoconstriction in children with asthma. *J Allergy Clin Immunol*. 2008; 12: 383-9.
367. Van der Wouden JC, Tasche MJ, Bernsen RM, Uijen JH, De Jongste JC, Ducharme FM. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev*. 2003; CD002173.
368. Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. *Pulm Pharmacol Ther*. 2009; 22(1): 9-19.
369. Bisgaard H, Le Roux P, Bjåmer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/Formoterol Maintenance Plus Reliever Therapy. A new strategy in pediatric asthma. *Chest*. 2006; 130: 1733-43.
370. Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Sträter C, Steinkamp G; VIAPAED Study Group. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatr Pulmonol*. 2009; 44(11): 1132-42.
371. Lemanske RF, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al.; Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung and Blood Institute. Stepup therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010; 362: 975-85.
372. Zeiger RS, Szeffler SJ, Phillips BR, Schatz M, Martinez F, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol*. 2006; 117: 45-52.
373. Van der Mark LB, Lyklema PHE, Geskus RB, Mohrs J, Bindels PJE, van Aalderen WMC, et al. A systematic review with attempted network meta-analysis of asthma therapy recommended for five to eighteen year olds in GINA steps three and four. *BMC Pulmonary Medicine*. 2012, 12: 63.
374. Seddon P, Bara A, Ducharme FM, Lasseresson TJ. Orat xanthines as maintenance treatment for asthma in children. *Cochrane Database of Systematic Reviews*. 2006; (1): CD002885.
375. Deschildre A, Marguet C, Salleron J, Pin I, Rittie JL, Derelle J, et al. Add-on omalizumab in children with severe allergic

- asthma: a 1-year real life survey. *Eur Respir J.* 2013; 42: 1224-33.
376. Fiocchi A, Fox AT. Preventing progression of allergic rhinitis: the role of specific immunotherapy. *Arch Dis Child Educ Pract Ed.* 2011; 96: 91-100.
377. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev.* 2003; (1): CD004107.
378. Ni Chroinin M, Greenstone IIG, Ducharme F. Addition of inhaled longacting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database of Systematic Reviews.* 2004; (4): CD005307.
379. Ducharme F, di Salvio F. Antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews.* 2004; (1): CD002314.
380. Bekhof J, Reimink R, Brand PL. Systematic review: insufficient validation of clinical scores for the assessment of acute dyspnoea in wheezing children. *Paediatr Respir Rev.* 2014; 15(1): 98-112.
381. Smith SR, Baty JD, Hodge D. Validation of the pulmonary score. An Asthma severity score for children. *Acad Emerg Med.* 2002; 9: 99-104.
382. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. *J Pediatr.* 1985; 106(4): 672-4.
383. Castro-Rodríguez JA, Rodrigo GJ. Beta-agonist through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age. A systematic review with meta-analysis. *J Pediatr.* 2004; 145: 172-7.
384. Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S, Samransamruajkit R. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer vs jet nebulizer in young children with wheezing. *Pediatr Pulmonol.* 2005; 39: 466-72.
385. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. *Acad Emerg Med.* 1996; 3(11): 1019-24.
386. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev.* 2013; (8): CD000060.
387. Everard ML, Bara A, Kurian M, Elliot TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years (Cochrane Review). In: *The Cochrane Library.* London: John Wiley & Sons Ltd; 2001.
388. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral Prednisolone for Preschool Children with Acute Virus-induced wheezing. *N Engl J Med.* 2009; 360(4): 329-38.
389. Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, et al. Oral versus intravenous corticosteroids in children hospitalised with asthma. *J Allergy Clin Immunol.* 1999; 103: 586-90.
390. Barnett PL, Caputo GL, Bassin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. *Ann Emerg Med.* 1997; 29: 212-7.
391. Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. *Chest.* 2002; 122: 624-8.
392. Beckhaus AA, Riutort MC, Castro-Rodríguez JA. Inhaled versus systemic corticosteroids for acute asthma in children. A systematic review. *Pediatr Pulmonol.* 2014; 49(4): 326-34.
393. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child.* 2005; 90: 74-7.
394. Geelhoed GC, Landau LI, Le Souef PN. Evaluation of SaO₂ as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med.* 1994; 23: 1236-41.
395. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, et al. Randomised controlled trial of high concentration versus tritated oxygen therapy in severe exacerbations of asthma. *Thorax.* 2011; 66: 937-41.
396. Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. *Acad Emerg Med.* 1997; 4(2): 114-7.
397. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008; 63(Suppl 86): 8-160.
398. Tomassen P, Newson RB, Hoffmans R, Lötvall J, Cardell LO, Gunnbjörnsdóttir M, et al. Reliability of EP30S symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis--a GA2 LEN study. *Allergy.* 2011; 66(4): 556-61.
399. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. *Otolaryngol--Head Neck Surg.* 2010; 143(1): 147-51.
400. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology.* 2012; 50(Suppl 23): 1-299.
401. Bousquet J, van Cauwenberge P, Khaltaev N; Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001; 108(5 Suppl): S147-334.
402. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallesi E, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy.* 2005; 60(7): 882-7.
403. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy.* 2005; 60(3): 350-3.
404. Valero A, Ferrer M, Sastre J, Navarro AM, Monclús L, Martí-Guadano E, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol.* 2007; 120(2): 359-65.
405. Valero A, Ferrer M, Baró E, Sastre J, Navarro AM, Martí-Guadano E, et al. Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis. *Allergy.* 2010; 65(12): 1609-13.
406. Montoro J, del Cuvillo A, Mullol J, Molina X, Bartra J, Dávila I, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. *Allergy.* 2012; 67(11): 1437-42.

407. Valero A, Muñoz-Cano R, Sastre J, Navarro AM, Martí-Guadaño E, Dávila I, et al. The impact of allergic rhinitis on symptoms, and quality of life using the new criterion of ARIA severity classification. *Rhinology*. 2012; 50(1): 33-6.
408. Rondón C, Campo P, Togiás A, Fokkens WJ, Durham SR, Powe DG, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. 2012; 129(6): 1460-7.
409. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004; 24(5): 758-64.
410. Pereira C, Valero A, Loureiro C, Dávila I, Martínez-Cócerca C, Murio C, et al. Iberian study of aeroallergens sensitisation in allergic rhinitis. *Eur Ann Allergy Clin Immunol*. 2006; 38(6): 186-94.
411. Navarro A, Colás C, Antón E, Conde J, Dávila I, Dordal MT, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergológica-2005. *J Investig Allergol Clin Immunol*. 2009; 19(Suppl 2): 7-13.
412. Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D, ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. 2008; 19(2): 110-24.
413. Gendo K, Larson EB. Evidence-based diagnostic strategies for evaluating suspected allergic rhinitis. *Ann Intern Med*. 2004; 140(4): 278-89.
414. Kerkhof M, Schouten JP, de Monchy JGR. The association of sensitization to inhalant allergens with allergy symptoms: the influence of bronchial hyperresponsiveness and blood eosinophil count. *Clin Exp Allergy*. 2000; 30(10): 1387-94.
415. Dordal MT, Lluch-Bernal M, Sánchez MC, Rondón C, Navarro A, Montoro J, et al. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol*. 2011; 21(1): 1-12.
416. Van Spronsen E, Ingels KJ, Jansen AH, Graamans K, Fokkens WJ. Evidence-based recommendations regarding the differential diagnosis and assessment of nasal congestion: using the new GRADE system. *Allergy*. 2008; 63(7): 820-33.
417. Valero A, Pereira C, Loureiro C, Martínez-Cócerca C, Murio C, Rico P, et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: a study of Spain and Portugal. *J Investig Allergol Clin Immunol*. 2009; 19(3): 167-72.
418. Del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients - The ADRIAL cohort study. *Rhinology*. 2010; 48(2): 201-5.
419. Leynaert B, Neukirch C, Kony S, Guénéguou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*. 2004; 113(1): 86-93.
420. Castillo JA, Mullol J. Comorbilidad de rinitis y asma en España (estudio RINAIR). *Arch Bronconeumol*. 2008; 44(11): 597-603.
421. Navarro AM, Valero A, Julia B, Quirze S. Coexistence of asthma and allergic rhinitis in adult patients attending clinics: ONEAIR Study. *J Investig Allergol Clin Immunol*. 2008; 18(4): 233-8.
422. Arnedo-Pena A, García-Marcos L, García G, Aguinagua I, González C, Morales M, et al. Time trends and geographical variations in the prevalence of symptoms of allergic rhinitis in 6-7-year-old children from eight areas of Spain according to the ISAAC. *An Pediatr Barc Spain*. 2005; 62(3): 229-36.
423. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008; 372: 1049-57.
424. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy*. 2008; 63(3): 292-8.
425. De Groot EP, Nijkamp A, Duiverman EJ, Brand PLP. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax*. 2012; 67(7): 582-7.
426. Oka A, Matsunaga K, Kamei T, Sakamoto Y, Hirano T, Hayata A, et al. Ongoing allergic rhinitis impairs asthma control by enhancing the lower airway inflammation. *J Allergy Clin Immunol Pract*. 2014; 2(2): 172-8.
427. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. *BMC Pulm Med*. 2006; 6(Suppl 1): S3.
428. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma*. 2006; 43(1): 1-7.
429. Boulay ME, Boulet LP. Lower airway inflammatory responses to repeated very-low-dose allergen challenge in allergic rhinitis and asthma. *Clin Exp Allergy*. 2002; 32(10): 1441-7.
430. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S, et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy*. 2000; 30(5): 663-9.
431. Kessel A. The impact of intranasal corticosteroids on lung function in children with allergic rhinitis. *Pediatr Pulmonol*. 2014; 49(9): 932-7.
432. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy*. 2013; 68(5): 569-79.
433. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010; 126(3): 466-76.
434. Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2007; 119: 157-64.
435. Owen CG, Shah A, Henshaw K, Smeeth L, Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. *Br J Gen Pract*. 2004; 54(503): 451-6.
436. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 Years of Age. *Chest*. 2008; 133: 599-609.
437. Rodrigo GJ, Neffen H, Castro Rodríguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011; 139: 28-35.
438. Wu W, Walters RD, Nadeau GA, Botnick W, Broughton N. An integrated analysis of the efficacy of fluticasone furoate nasal

- spray versus placebo on the nasal symptoms of perennial allergic rhinitis. *Allergy Asthma Proc.* 2013; 34(3): 283-91.
439. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol.* 2012; 129(5): 1282-9.
440. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, et al. Clinically relevant effect of a new intranasal therapy (MP29- 02) in allergic rhinitis assessed by responder analysis. *Int Arch Allergy Immunol.* 2013; 161(4): 369-77.
441. Mortuaire G, de Gabory L, François M, Massé G, Bloch F, Brion N, et al. Rebound congestion and rhinitis medicamentosa: nasal decongestants in clinical practice. Critical review of the literature by a medical panel. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2013; 130(3): 137-44.
442. Dal Negro R, Piskorz P, Vives R, Guilera M, Sazonov V, Badia X. Healthcare utilisation and costs associated with adding montelukast to current therapy in patients with mild to moderate asthma and co-morbid allergic rhinitis: PRACTICAL study. *Pharmacoeconomics.* 2007; 25(8): 665-76.
443. Keith PK, Koch C, Djandji M, Bouchard J, Psaradellis E, Sampalis JS, et al. Montelukast as add-on therapy with inhaled corticosteroids alone or inhaled corticosteroids and long-acting beta-2-agonists in the management of patients diagnosed with asthma and concurrent allergic rhinitis (the RADAR trial). *Can Respir J.* 2009; 16(Suppl A): 17A-31A.
444. Kaiser HB, Findlay SR, Georgitis JW, Grossman J, Ratner PH, Tinkelman DG, et al. The anticholinergic agent, ipratropium bromide, is useful in the treatment of rhinorrhea associated with perennial allergic rhinitis. *Allergy Asthma Proc.* 1998; 19(1): 23-9.
445. AlBalawi ZH, Othman SS, Alfaleh K. Intranasal ipratropium bromide for the common cold. *Cochrane Database Syst Rev.* 2013; (6): CD008231.
446. Tsubouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract.* 2014; 2(3): 332-40.e1.
447. Kim JM, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics.* 2013; 131(6): 1155-67.
448. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess Winch Engl.* 2013; 17(27): vi, xi- xiv, 1-322.
449. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco ADR, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol.* 2008; 101(2): 206-11.
450. Voltolini S, Troise C, Incorvaia C, Bignardi D, Di Cara G, Marcucci F, et al. Effectiveness of high dose sublingual immunotherapy to induce a stepdown of seasonal asthma: a pilot study. *Curr Med Res Opin.* 2010; 26(1): 37-40.
451. De Castro G, Zicari AM, Indinnimeo L, Tancredi G, di Coste A, Occasi F, et al. Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life. *Eur Rev Med Pharmacol Sci.* 2013; 17(16): 2225-31.
452. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. *Allergy.* 2012; 67(2): 158-65.
453. Izquierdo-Domínguez A, Valero AL, Mulla J. Comparative analysis of allergic rhinitis in children and adults. *Curr Allergy Asthma Rep.* 2013; 13(2): 142-51.
454. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy.* 2013; 68(9): 1102-16.
455. Alobid I, Antón E, Armengot M, Chao J, Colás C, del Cuvillo A, et al. SEAIC-SEORL. Consensus Document on Nasal Polyposis. POLINA Project. *J Investig Allergol Clin Immunol.* 2011; 21(Suppl 1): 1-58.
456. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chantal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. *Allergy.* 2005; 60(2): 233-7.
457. Johansson L, Akerlund A, Holmberg K, Melén I, Bende M. Prevalence of nasal polyps in adults: the Skövde population-based study. *Ann Otol Rhinol Laryngol.* 2003; 112(7): 625-9.
458. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: The GA2LEN survey in Europe. *Allergy.* 2012; 67: 91-8.
459. Muñoz F, Jurado-Ramos A, Fernández-Conde BL, Soler R, Barasona MJ, Cantillo E, et al. Allergenic profile of nasal polyposis. *J Investig Allergol Clin Immunol.* 2009; 19(2): 110-6.
460. Pérez de Llano L, Vennera MC, Alvarez Effects of omalizumab in non-atopic asthma: results from a Spanish multicenter registry. *J Asthma.* 2013; 50(3): 296-301.
461. Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *Am J Rhinol Allergy.* 2011; 25(4): 205-8.
462. Staikūniene J, Vaitkus S, Japertiene LM, Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: clinical and radiological features, allergy and inflammation markers. *Med Kaunas Lith.* 2008; 44(4): 257-65.
463. Ehnhage A, Olsson P, Kölbeck K-G, Skedinger M, Stjärne P, NAFS Study Group. One year after endoscopic sinus surgery in polyposis: asthma, olfaction, and quality-of-life outcomes. *Otolaryngol-Head Neck Surg.* 2012; 146(5): 834-41.
464. Wuister AMH, Goto NA, Oostveen EJ, de Jong WU, van der Valk ES, Kaper NM, et al. Nasal endoscopy is recommended for diagnosing adults with chronic rhinosinusitis. *Otolaryngol-Head Neck Surg.* 2014; 150(3): 359-64.
465. Shahizon AMM, Suraya A, Rozmnan Z, Aini AA, Gendeh BS. Correlation of computed tomography and nasal endoscopic findings in chronic rhinosinusitis. *Med J Malaysia.* 2008; 63(3): 211-5.
466. Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ. Topical steroids for nasal polyps. *Cochrane Database Syst Rev Online.* 2012; (12): CD006549.
467. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. *Cochrane Database Syst Rev Online.* 2006; (3): CD004458.
468. Dalziel K, Stein K, Round A, Garside R, Royle P. Endoscopic sinus surgery for the excision of nasal polyps: A systematic

- review of safety and effectiveness. *Am J Rhinol*. 2006; 20(5): 506-19.
469. Vashishta R, Soler ZM, Nguyen SA, Schlosser RJ. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2013; 3(10): 788-94.
 470. Martínez-Devesa P, Patiar S. Oral steroids for nasal polyps. *Cochrane Database Syst Rev Online*. 2011; (7): CD005232.
 471. Wentzel JL, Soler ZM, DeYoung K, Nguyen SA, Lohia S, Schlosser RJ. Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review. *Am J Rhinol Allergy*. 2013; 27(6): 482-9.
 472. Gevaert P, Calus L, Van Zele T, Blomme K, de Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013; 131(1): 110-6.e1.
 473. Hardin M, Silverman E, Barr G, Hansel N, Schroeder J, Make B, et al.; for the COPDGene Investigators. The clinical features of the overlap between COPD and asthma. *Respiratory Research*. 2011; 12: 127.
 474. Menezes AM, Montes de Oca M, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al.; PLATINO team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPS-Asthma. *Chest*. 2014; 145(2): 297-304.
 475. Jamieson D, Matsui E, Belli A, McCormack M, Peng E, Pierre-Louis S, et al. Effects of Allergic Phenotype on Respiratory Symptoms and Exacerbations in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2013; 188: 187-92.
 476. Lee J, Haselkorn T, Borish L, Rasouliyan L, Chipps B, Wenzel S. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma. *Chest*. 2007; 132: 1882-9.
 477. Brightling CE, McKenna S, Hargadon B, Birring S, Green R, Siva R, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease *Thorax*. 2005; 60: 193-98.
 478. Fujimoto K, Kubo K, Yamamoto H, Yamaguchi S, Matsuzawa Y. Eosinophilic Inflammation in the Airway Is Related to Glucocorticoid Reversibility in Patients With Pulmonary Emphysema. *Chet*. 1999; 115: 697-702.
 479. Kitaguchi Y, Konatsu Y, Fujimoto K, Hanaoka M, Kubo K. Sputum eosinophilia can predict responsiveness to inhaled corticosteroid treatment in patients with overlap syndrome of COPD and asthma. *Intern J COPD*. 2012; 7: 283-9.
 480. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, et al.; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol*. 2013; pii: S0091-6749(13)01563-7.
 481. Pavord ID, Thomson NC, Niven RM, Corris PA, Chung KF, Cox G, et al. Research in Severe Asthma (RISA) Trial Study Group. Safety of bronchial hermoplasty in patients with severe refractory asthma. *Ann Allergy Asthma Immunol* 2013; 111(5): 402-7.
 482. Calverley P, Albert P, Walker P. Bronchodilator reversibility in chronic obstructive pulmonary disease: use and limitations. *Lancet Respir Med*. 2013; 1: 564-73.
 483. Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1985; 132: 25-9.
 484. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013; 368(26): 2455-66.
 485. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet*. 1999; 353: 2213-4.
 486. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, Solberg OD, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol*. 2012; 130: 647-54.
 487. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013; 68(11): 1029-36.
 488. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al.; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008; 359(15): 1543-54.
 489. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012; 367(13): 1198-207.
 490. Bousquet J, Aubier M, Sastre J, Izquierdo JL, Adler LM, Hofbauer P, et al. Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma. *Allergy*. 2006; 61: 72-8.
 491. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martínez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009; 374: 685-94.
 492. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest*. 2013; 144(4): 1222-9.
 493. Agustí A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *Eur Respir J*. 2014; 43(3): 763-72.
 494. Serra-Batlles J, Plaza V, Morejón E, Comella A, Brugués J. The costs of asthma according to the degree of severity. *Eur Respir J*. 1998; 12: 1322-6.
 495. Martínez-Moragón E, Serra- Batllés J, de Diego A, Palop M, Casan P, Rubio-Terrés C, et al.; por el grupo de Investigadores del estudio AsmaCost. Economic cost of treating the patient with asthma in Spain: the AsmaCost study. *Arch Bronconeumol*. 2009; 45: 481-6.
 496. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk J, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014; 43: 343-73.
 497. Barranco P, Pérez-Francis C, Quirce S, Gómez-Torrijos E, Cárdenas R, Sánchez-García S, et al. Severe Asthma Working Group of the SEAIC Asthma Committee. Consensus Document on the Diagnosis of Severe Uncontrolled Asthma. *J Investig Allergol Clin Immunol*. 2012; 22: 460-75.
 498. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Verrisnel J, et al.; on behalf of the members of the Unbiased Biomarkers for

- the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation. *Thorax*. 2011; 66: 910-17.
499. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol*. 2010; 126: 926-38.
 500. Quirce S, Plaza V, Picado C, Vennera M, Casafont J. Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain. *J Investig Allergol Clin Immunol*. 2011; 21: 466-71.
 501. Keenan CR, Salem S, Fietz ER, Gualano RC, Stewart AG. Glucocorticoid-resistant asthma and novel anti-inflammatory drugs. *Drug Discovery Today*. 2012; 17: 1031-8.
 502. Barnes PJ, Greening AP, Crompton GK. Glucocorticoid resistance in asthma. *Am J Respir Crit Care Med*. 1995; 152: S125-S140.
 503. Woolcock AJ. Corticosteroid-resistant asthma. Definitions. *Ann J Respir Crit Care Med*. 1996; 154: S45-S48.
 504. Reddy D, Little F. Glucocorticoid-resistant asthma: more than meets the eye. *J Asthma*. 2013; 50(10): 1036-44.
 505. Bhakta NR, Woodruff PG. Human asthma phenotypes: from the clinic, to cytokines, and back again. *Immunol Rev*. 2011; 242 (1): 220-32.
 506. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008; 178: 218-24.
 507. Siroux V, Basagaña X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J*. 2011; 38: 310-7.
 508. Lotvall J, Akdis A, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011; 127: 533-60.
 509. Agache IO. From phenotypes to endotypes to asthma treatment. *Curr Opin Allergy Clin Immunol*. 2013; 13: 249-56.
 510. Cisneros C. Normativa SEPAR del asma grave no controlada. *Arch Bronconeumol* 2015. Disponible en <http://www.elsevierinstituciones.com/ficheros/eop/S0300-2896%2814%2900492-X.pdf> (Última visita el 30 de marzo de 2015).
 511. Martinez FD, Vercell D. Asthma. *Lancet*. 2013; 382: 1360-72.
 512. Erzurum SC, Gaston BM. Biomarkers in asthma: a real hope to better manage asthma. *Clin Chest Med*. 2012; 33(3): 459-71.
 513. Brusselle GG, Maes T, Bracke KR. Eosinophilic airway inflammation in nonallergic asthma. *Nature Medicine*. 2013; 19(8): 977-9.
 514. Green RH. Analysis of induced sputum in adults with asthma: identificación of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax*. 2002; 57: 875-9.
 515. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax*. 2003; 58: 561-6.
 516. Robinson DS, Campbell DA, Durham SR, Pfeiffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J*. 2003; 22: 478-83.
 517. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, et al.; Canadian Respiratory Clinical Research Consortium. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ*. 2008; 179: 1121-31.
 518. Gibeon D, Chung KF. The investigation of severe asthma to define phenotypes. *Clin Exp Allergy*. 2012; 42: 678-92.
 519. Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med*. 2011; 105: 1308-15.
 520. Bilodeau L, Boulay ME, Prince P, Boisvert P, Boulet LP. Comparative clinical and airway inflammatory features of asthmatics with or without polyps. *Rhinology*. 2010; 48: 420-5.
 521. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax*. 2010; 65: 787-94.
 522. Moore WC, Bleecker ER, Curran- Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007; 119(2): 405-13.
 523. Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, et al. Lack of control of severe asthma is associated with co-existence of moderate-severe rhinitis. *Allergy*. 2008; 63: 564-9.
 524. Ten Brinke A, Grootendorst DC, Schmidt JT, de Bruïne FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol*. 2002; 109: 621-6.
 525. ENFUMOSA. European Network for Understanding Mechanisms of Severe Asthma. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J*. 2003; 22: 470-7.
 526. ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med*. 2001; 164: 744-8.
 527. Lavoie KL, Bouthillier D, Bacon SL, Lemièrre C, Martin J, Hamid Q, et al. Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma. *Chest*. 2010; 137: 1324-31.
 528. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control and inflammation. *J Allergy Clin Immunol*. 2011; 128: 508-15.
 529. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol*. 2011; 127: 1486-93.
 530. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemièrre C, et al. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol*. 2009; 124: 371-6.
 531. Sharma B, Feinsilver S, Owens RL, Malhotra A, Mcsharry D, Karbowitz S. Obstructive airway disease and obstructive sleep apnea: effect of pulmonary function. *Lung*. 2011; 189: 37-41.
 532. Low K, Lau KK, Holmes P, Crossett M, Vallance N, Phyland D, et al. Abnormal vocal cord function in difficult-to-treat asthma. *Am J Respir Crit Care Med*. 2011; 184: 50-6.

533. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG; National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol.* 2006; 118: 1218-25.
534. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med.* 1991; 324: 359-63.
535. Almqvist C, Wickman M, Perfetti L, Berglind N, Renström A, Hedrén M, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med.* 2001; 163: 694-8.
536. Gruchalla RS, Pongracic J, Plaut M. Inner city asthma study: relationships among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol.* 2005; 115: 478-85.
537. Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A, Custovic A. Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *J Allergy Clin Immunol.* 2003; 112: 362-8.
538. Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold *Alternaria alternata*. *J Allergy Clin Immunol.* 2007; 120: 610-7.
539. Chester DA, Hanna EA, Pickelman BG, Rosenman KD. Asthma death after spraying polyurethane truck bedliner. *Am J Ind Med.* 2005; 48: 78-84.
540. Henneberger PK, Mirabelli MC, Kogevinas M, Antó JM, Plana E, Dahlman-Högglund A, et al. The occupational contribution to severe exacerbation of asthma. *Eur Respir J.* 2010; 36: 743-50.
541. Le Moual N, Siroux V, Pin I, Kauffman F, Kennedy S. Asthma severity and exposure to occupational asthmagens. *Am J Respir Crit Care Med.* 2005; 172: 440-5.
542. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med.* 2005; 62: 290-9.
543. Ortega HG, Kreiss K, Schill DP, Weissman DN. Fatal asthma from powdering shark cartilage and review of fatal occupational asthma literature. *Am J Ind Med.* 2002; 42: 50-4.
544. Everard ML. The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allergy Clin Immunol.* 2006; 6: 56-61.
545. Murray CS, Poletti G, Kebabdzic T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax.* 2006; 61: 376-82.
546. Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *Eur Respir J.* 2002; 19: 68-75.
547. Fauroux B, Sampil M, Quénel P, Lemoullec Y. Ozone: a trigger for hospital pediatric asthma emergency room visits. *Pediatr Pulmonol.* 2000; 30: 41-6.
548. Feo Brito F, Mur Gimeno P, Martínez C, Tobías A, Suárez L, Guerra F, et al. Air pollution and seasonal asthma during the pollen season. A cohort study in Puertollano and Ciudad Real (Spain). *Allergy.* 2007; 62: 1152-7.
549. Galan I, Tobias A, Banegas JR, Arangué E. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J.* 2003; 22: 1-7.
550. Mur Gimeno P, Feo Brito F, Martínez C, Tobías A, Suárez L, Guerra F, et al. Decompensation of pollen-induced asthma in two towns with different pollution levels in La Mancha, Spain. *Clin Exp Allergy.* 2007; 37: 558-63.
551. Schwartz J, Slater D, Timothy V, Larson T, William E, Keonig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis.* 1993; 147: 826-31.
552. Jenkins K, Costello J, Hodge L. Systematic review of prevalence of aspirin-induced asthma and its implications for clinical practice. *BMJ.* 2004; 328: 434-7.
553. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy.* 2005; 60: 302-8.
554. Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY, et al.; Daclizumab Asthma Study Group. Daclizumab improves asthma control in patients with moderate to severe persistent asthma. *Am J Respir Crit Care Med.* 2008; 178: 1002-8.
555. Castro M, Mathur s, Hargreave F, Boulet LP, Xie F, Young J, et al.; Res-5-0010 Study Group. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med.* 2011; 184: 1125-32.
556. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011; 365: 1088-98.
557. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Eng J Med.* 2009; 360: 973-84.
558. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol.* 2013; 132: 1086-96.
559. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLoS One.* 2013; 8: e59872.
560. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol.* 2004; 113: 101-8.
561. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Eng J Med.* 2009; 360: 985-93.
562. Wenzel SE, Barnes PJ, Bleeker ER, Bousquet J, Busse W, Dahlén SE, et al.; T03 Asthma Investigators. A randomized, double-blind, placebo-controlled study of tumor necrosis factor alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med.* 2009; 179: 549-58.
563. Kerstjens HA, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol.* 2011; 128: 308-14.
564. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for

- adults with uncontrolled asthma. *N Engl J Med.* 2010; 363: 1715-26.
565. Tian JW, Chen JW, Chen X. Tiotropium versus placebo for inadequately controlled asthma. A meta-analysis. *Respir Care.* 2014; 59(5): 654-66.
566. Adams NP, Bestall JC, Jones P, Lasserson TJ, Griffiths B, Cates CJ. Fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2008; (4): CD003534.
567. Bateman ED. Eficacia y seguridad de ciclesonida en dosis altas en el tratamiento del asma grave. *Expert Rev Respir Med.* 2013; 7(4): 339-48.
568. Amelink M, Hashimoto S, Spinhoven P, Pasma HR, Sterk PJ, Bel EH, Ten Brinke A. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. *Respir Med.* 2014; 108: 438-44.
569. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standar therapy; a randomized trial. *Ann Intern Med.* 2011; 154: 573-82.
570. Matthews JG. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011; 365: 1088-98.
571. Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* 2013; 41: 330-8.
572. Moss RB. Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis. *Eur Respir J.* 2014; 43(5): 1487-500.
573. Dahlen SE, Malmstrom K, Nizankowska E, Dahlen B, Kuna P, Kowalski M, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002; 165: 9-14.
574. Dias-Júnior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A. Effects of weight loss on asthma control in obese patients with severe asthma. *Eur Respir J.* 2014; 43(5): 1368-77.
575. Ojirala RG, Aldrich TK, Prezant DJ, Sinnett MJ, Enden JB, Williams MH Jr. High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N Engl J Med.* 1991; 324: 585-9.
576. Ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Cir Care Med.* 2004; 170: 601-5.
577. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al.; AIR Trial StudyGroup. Asthma control during the year after bronchial thermoplasty. *N Engl J Med.* 2007; 356(13): 1327-37.
578. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Research in SevereAsthma (RISA) Trial Study Group. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med.* 2007; 176(12): 1185-91.
579. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al; Asthma Intervention Research (AIR) 2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: amulticenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med.* 2010; 181(2): 116-24.
580. Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, et al. AIR Trial StudyGroup. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. *BMC Pulm Med.* 2011; 11: 8.
581. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Asthma Intervention Research (AIR) 2 Trial Study Group. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol.* 2013; 132(6): 1295-302.
582. Pavord ID. Complex airway disease: an approach to assessment and management. *Lancet Respir Med.* 2013; 31; 1(1): 84-90.
583. Torrego A, Solà I, Munoz AM, Roqué i Figuls M, Yepes-Nuñez JJ, Alonso-Coello P, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. *Cochrane Database of Systematic Reviews.* 2014; (3): CD009910.
584. Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults. *Cochrane Database Syst Rev.* 2000; (2): CD000391.
585. Hedlin G, Bush A, Lodrup-Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J.* 2010; 36: 196-201.
586. Bush A, Saglani S. Management of severe asthma in children. *Lancet.* 2010; 376: 814-25.
587. Saglani S, Lenney W. Difficult asthma in the pre-school child. *Paed Respir Rev.* 2004; 5: 199-206.
588. Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E, et al. The importance de nurse-led home visits in the assessment of children with problematic asthma. *Arch dis Child.* 2009; 94: 780-4.
589. Baraldi E, Donegà S, Carraro S, Farina M, Barbato A, Cutrone C. Tracheobronchomalacia in wheezing Young children poorly responsive to asthma therapy. *Allergy.* 2010; 65: 1058-72.
590. De Baets F, de Schutter I, Aarts C, Haerynck F, van daele S, de Wachter, et al. Malacia, inflammation and bronchoalveolar lavage culture in children with persistent respiratory symptoms. *Eur Respir J.* 2012; 39: 392-5.
591. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med.* 2012; 33: 785-95.
592. Walia M, Paul L, Satyavani A, Lodha R, Kalaivani M, Kabra SK. Assessment of inhalation technique and determinants of incorrect performance among children with asthma. *Pediatr Pulmonol.* 2006; 41: 1082-87.
593. Suárez RG, Galván C, Oliva C, Aguirre A, Vázquez C; Grupo de Trabajo sobre Tabaquismo de la Infancia y Adolescencia de la Sociedad Española de Neumología Pediátrica. Exposición pasiva al humo del tabaco del niño asmático y su asociación con la gravedad del asma. *An Pediatr (Barc).* 2013; 78: 35-42.
594. Sales J, Fivush R, Teague GW. The role of parental coping in children with asthma's psychological well-being and asthma-related quality of life. *J Pediatr Psychol.* 2008; 33: 208-19.
595. Bush A, Pedersen S, Hedlin G et al. Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where? *Eur Respir J* 2011; 38: 947-58.
596. Quirce S, Bobolea I, Dominguez-Ortega J, Barranco P. Futuras terapias biológicas en el asma. *Arch Bronconeumol.* 2014; 50(8): 355-61.
597. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled

- corticosteroids in the United Kingdom. *Arch Dis Child*. 2002; 87: 457-61.
598. Busse WW1, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti- IgE) for asthma in inner-city children. *N Engl J Med*. 2011; 364: 1005–15.
 599. Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy*. 2011; 41(2): 160-70.
 600. Panickar JR, Kenia P, Silverman M, Grigg J. Intramuscular triamcinolone for difficult asthma. *Pediatr Pulmonol*. 2005; 39: 421-5.
 601. Strunk RC, Bacharier LB, Philips BR, Szeffler SJ, Zeiger RS, Chinchilli VM, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol*. 2008; 122: 1138-44.
 602. Schwerk N, Brinkmann F, Soudah B, Kabesch M, Hansen G. Wheeze in Preschool Age Is Associated with Pulmonary Bacterial Infection and Resolves after Antibiotic Therapy. *PLoS One*. 2011; 6(11): e27913.
 603. De Schutter I, Dreesman A, Soetens O, de Waele M, Crokaert F, Verhaegen J, et al. In young children, persistent wheezing is associated with bronchial bacterial infection: a retrospective analysis. *BMC Pediatr*. 2012; 22: 12: 83.
 604. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. *Immunol Allergy Clin North Am*. 2006; 26(1): 63-80.
 605. Clifton V. Maternal asthma during pregnancy and fetal outcomes: potential mechanisms and possible solutions. *Curr Opin Allergy Clin Immunol*. 2006; 6(5): 307-11.
 606. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006; 61(2): 169-76.
 607. Wang G, Murphy VE, Namazy J, Powell H, Schatz M, Chambers C, et al. The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet*. 2014; 27(9): 934-42.
 608. Murphy VE, Gibson PG. Asthma in pregnancy. *Clin Chest Med*. 2011; 32(1): 93-110.
 609. Murphy VE, Schatz M. Asthma in pregnancy: a hit for two. *Eur Respir Rev*. 2014; 23(131): 64-8.
 610. Lim A, Stewart K, König K, George J. Systematic review of the safety of regular preventive asthma medications during pregnancy. *Ann Pharmacother*. 2011; 45(7-8): 931-45.
 611. Wendel PJ, Ramin SM, Barnett Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. *Am J Obstet Gynecol*. 1996; 175(1): 150-4.
 612. Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2005; 95(3): 234-8.
 613. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy Clin Immunol*. 2005; 115(1): 34-46.
 614. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonid in early pregnancy. *Obstet. Gynecol*. 1999; 93: 392-5.
 615. Eltonsy S, Kettani F-Z, Blais L. Beta2-agonists use during pregnancy and perinatal outcomes: a systematic review. *Respir Med*. 2014; 108(1): 9-33.
 616. Bakhireva LN, Schatz M, Chambers CD. Effect of maternal asthma and gestational asthma therapy on fetal growth. *J Asthma*. 2007; 44 (2): 71-6.
 617. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011; 378(9795): 983-90.
 618. Moscato G, Pala G, Barnig C, De Blay F, Del Giacco SR, Folletti I, et al. EAACI consensus statement for investigation of work-related asthma in non-specialized centres *Allergy*. 2012; 67: 491-501.
 619. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet*. 2007; 370: 336-41.
 620. Tarlo SM, Lemier C. Occupational asthma. *N Engl J Med*. 2014; 370; 7: 640-9.
 621. Brooks SM, Weiss MA, Berstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest*. 1985; 88: 376-84.
 622. Tarlo SM, Broder I. Irritant-induced occupational asthma. *Chest*. 1989; 96: 297-300.
 623. Heederik D, Henneberg PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir Rev*. 2012; 21: 112-24.
 624. Kern DG. Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. *Am Rev Respir Dis*. 1991; 144: 1058-64.
 625. Gautrin D, Ghezzi H, Infante Rivard C, Malo JL. Incidence and determinants of IgE-mediated sensitization in apprentices: a prospective study. *Am J Respir Crit. Care Med*. 2000; 162: 1222-8.
 626. Tarlo SM, Balmes J, Balkisson R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and Management of Work Related Asthma. American College of Chest Physicians Consensus Statement. *Chest*. 2008; 134: 1S-41S.
 627. Adishes A, Gruszka L, Robinson E, Evans G. Smoking status and immunoglobulin E seropositivity to workplace allergens. *Occup Med (Lond)*. 2011; 61: 62-4.
 628. Vandenas O, Ghezzi H, Munoz X, Moscato G, Perfetti L, Lemièrre C, et al . What are the questionnaire items most useful in identifying subjects with occupational asthma? *Eur Respir J*. 2005; 26: 1056-63.
 629. Cruz MJ, Munoz X. The current diagnostic role of the specific occupational laboratory challenge test. *Curr Opin Allergy Clin Immunol*. 2012; 12: 119-25.
 630. Cote J, Kennedy S, Cha-Yeung M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. *J Allergy Clinical Immunol*. 1990; 85: 592-8.
 631. Cartier A, Sastre J. Clinical assessment of occupational asthma and its differential diagnosis. *Immunol Allergy Clin North Am*. 2011; 31: 717-28.
 632. De Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwiers D, Frings-Dresen MH, et al. Workplace interventions for treatment of occupational asthma . *Cochrane Database Syst Rev*. 2011; (5): CD006308.

633. Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemier C, Martin J, et al. An Official American Thoracic Society Statement: Work- Exacerbated Asthma. *AM J Respir Crit Care Med.* 2011; 184: 368-78.
634. Parsons JP, Kaeding C, Phillips G, Jarloura D, Wadley G, Mastrorarde JG. Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. *Med Sci Sports Exerc.* 2007; 39: 1487-92.
635. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol.* 2008. 122: 225-35.
636. Cienciewicki J, Trivedi S, Kleeberger SR. Oxidants and the pathogenesis of lung diseases. *J Allergy Clin Immunol.* 2008; 122: 456-68.
637. De Baets F, Bodart E, Dramaix-Wilmet M, Van Daele S, de Bilderling G, Masset S, et al. Exercise-induced respiratory symptoms are poor predictors of bronchoconstrictions. *Pediatr Pulmonol.* 2005; 39: 301-5.
638. Weimberger M, Abu- Hasan M. Perceptions and pathophysiology of dyspnea and exercise intolerance. *Pediatr Clin North Am.* 2009; 56: 33-48.
639. Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capão-Filipe M, et al. American Academy of Allergy, Asthma and Immunology Work Group report: exercise-induced asthma. *J Allergy Clin Immunol.* 2007; 119: 1349-58.
640. Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise induced bronchoconstriction in athletes. *J Allergy Clin Immunol.* 2008; 122: 238-48.
641. Dryden DM, Spooner CH, Stickland MK, Vandermeer B, Tjosvold L, Bialy L, Wong K, Rowe BH. Exercise-induced bronchoconstriction and asthma. *Evid Rep Technol Assess (Full Rep).* 2010; 189: 1-154.
642. Weinberger M. Long-acting beta-agonists and exercise. *J Allergy Clin Immunol.* 2008; 122: 251-3.
643. Kippelen P, Larsson J, Anderson SD, Brannan JD, Delin I, Dahlen B, et al. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. *Med Sci Sports Exerc.* 2010; 42: 273-80.
644. Philip G, Pearlman DS, Villaran C, Legrand C, Loeys T, Langdon RB, et al. Single-dose montelukast or salmeterol as protection against exercise-induced bronchoconstriction. *Chest.* 2007; 132: 875-83.
645. Ram FS, Robinson SM, Black PN, Picot J. Physical training for asthma. *Cochrane Database Syst Rev.* 2005; (5) CD001116.
646. Stickland MK, Rowe BH, Spooner CH, Vandermeer B, Dryden DM. Effect of warm-up exercise on exercise-induced bronchoconstriction. *Med Sci Sports Exerc.* 2012; 44: 389-91.
647. Mickleborough TD. A nutritional approach to managing exercise-induced asthma. *Exerc Sport Sci Rev.* 2008; 36: 135-44.
648. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin exacerbated respiratory disease. *Ann Allergy Asthma Immunol.* 2002; 89: 472-8.
649. Fahrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol.* 2003; 24: 113-24.
650. Delaney JC. The diagnosis of aspirin idiosyncrasy by analgesic challenge. *Clin Allergy.* 1976; 6: 177-81.
651. Vally H, Taylor ML, Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax.* 2002; 57: 569-74.
652. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol.* 2003; 111: 913-21.
653. Ying S, Corrigan CJ, Lee TH. Mechanisms of aspirin sensitive asthma. *Allergology International.* 2008; 53: 111-9.
654. Sousa A, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene receptor expression on nasal mucosa inflammatory cells in aspirin sensitive rhinosinusitis. *N Engl J Med.* 2002; 347: 1524-6.
655. Makoswka JS, Grzegorzczak J, Bienkiewicz B, Wozniak M, Kowalski ML. Systemic responses after bronchial aspirin challenges in sensitive patients with asthma. *J Allergy Clin Immunol.* 2008; 121: 348-54.
656. Sanak M, Pierzchalska M, Bazan-Socha S, Szczeklik A. Enhanced expression of the leukotriene E 4 synthase due to overactive transcription of an allelic variant associated with aspirin intolerant asthma. *Am J Respir Cell Mol Biol.* 2000; 23: 290-6.
657. Szczeklik A, Sanak M. Genetic mechanism in aspirin-induced asthma. *Am J Respir Crit Care Med.* 2000; 161: S142-6.
658. Alonso-Llamazares A, Martinez-Cóccera C, Dominguez-Ortega J, Robledo-Echarren T, Cimarra-Alvarez M, Mesa del Castillo M. Nasal Provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy.* 2002; 57: 632-5.
659. Barranco P, Bobolea I, Larco JI, Prior N, López-Serrano MC, Quirce S. Diagnosis of Aspirin-Induced Asthma Combining the Bronchial and the Oral challenge Tests: A pilot study. *J Investig Allergol Clin Immunol.* 2009; 19: 446-52.
660. Nizankowska E, Bestynska Krypela A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J.* 2000; 15: 863-9.
661. Hosemann W. Surgical treatment of nasal polyposis in patients with aspirin intolerance. *Thorax.* 2000; 55: 87-90.
662. Stevenson DD. Aspirin and NSAID sensitivity. *Immunol Allergy Clin North Am.* 2004; 24: 491-505.
663. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2003; 111: 180-6.
664. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy.* 2007; 27(6): 852-9.
665. Antczak A, Montuschi P, Kharitonov S, Gorski P, Barnes PJ. Increased exhaled cysteinyl-leukotrienes and 8-isoprostane in aspirin-induced asthma. *Am J Respir Crit Care Med.* 2002; 166: 301-6.
666. Dahlén B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med.* 1998; 157: 1187-94.
667. Dahlén SE, Malmstrom K, Nizankowska E. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002; 165: 9-14.

668. Lee DK, Haggart K, Robb FM, Lipworth BJ. Montelukast protects against nasal lysine-aspirin challenge in patients with aspirin-induced asthma. *Eur Respir J*. 2004; 24: 226-30.
669. Fischer TJ, Guilfoile TD, Kesarwala HH, Winant JG Jr, Kearns GL, Gartside PS, et al. Adverse pulmonary responses to aspirin and acetaminophen in chronic childhood asthma. *Pediatrics*. 1983; 71: 313-8.
670. Settupane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross-sensitivity with acetaminophen in aspirin sensitive asthmatics subjects. *J Allergy Clin Immunol*. 1995; 96: 480-5.
671. Valero A, Baltasar M, Enrique E, Pau L, Dordal MT, Cisteró A, et al. NSAID-sensitive patients tolerate rofecoxib. *Allergy*. 2002; 57: 1214-5.
672. El Miedany Y, Youssef S, Ahrned I, El Gaafary M. Safety of etoricoxib a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2006; 97: 105-9.
673. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. *J Allergy Clin Immunol*. 2014; 134(1): 40-5.
674. Stevenson DD, Pleskow WW, Simon RA, Mathison DA, Lumry WR, Schatz M, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. *J Allergy Clin Immunol*. 1984; 73: 500-7.
675. Rozsasi A, Polzehl D, Deutschle T, Smith E, Wiesmiller K, Riechelmann H, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy*. 2008; 63: 1228-34.
676. Williams AN, Woessner KM. The clinical effectiveness of aspirin desensitization in chronic rhinosinusitis. *Curr Allergy Asthma Rep*. 2008; 8: 245-52.
677. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test for diagnosis of aspirin-induced asthma. *J Allergy Clin Immunol*. 1998; 101: 581-6.
678. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J Allergy Clin Immunol*. 1982; 69: 11-9.
679. Kenn K, Balkissoon R. Vocal Cord Dysfunction: What Do We Know? *Eur Respir*. 2011; 37(1): 194-200.
680. Giménez LM, Zafra H. Vocal cord dysfunction: an update. *Ann Allergy Asthma Immunol*. 2011; 106 (4): 267-74.
681. Morris MJ, Christopher KL. Diagnostic Criteria for the Classification of Vocal Cord Dysfunction. *Chest*. 2010; 138(5): 1213-23.
682. Sanz S, López VA, Almería E, Villa JR. Spirometry patterns in vocal cord dysfunction. *Anales de pediatría*. 2013; 78(3): 173-77.
683. Christensen PM, Maltbæk N, Jørgensen IM, Nielsen KG. Can Flow Volume Loops Be Used to Diagnose Exercise Induced Laryngeal Obstructions? A Comparison Study Examining the Accuracy and Inter Rater Agreement of Flow Volume Loops as a Diagnostic Tool. *Prim Care Respir J*. 2013; 22 (3): 306-11.
684. Traister RS, Fajt ML, Landsittel D, Petrov AA. A Novel Scoring System to Distinguish Vocal Cord Dysfunction from Asthma. *J Allergy Clin Immunol*. In Practice. 2014; 2(1): 65-9.
685. Praveen B, Kaliner M. Vocal Cord Dysfunction Treatment & Management. 2014. <http://emedicine.medscape.com/article/137782-treatment> (Última visita el 30 de marzo de 2015).
686. Kryworuchko J, Stacey D, Bai N, Graham ID. Twelve years of clinical practice guideline development, dissemination and evaluation in Canada (1994 to 2005). *Implement Sci*. 2009; 4: 49.
687. Plaza V, Bellido-Casado J, Alonso-Coello P, Rodrigo G. Guías de Práctica Clínica para el asma. Luces y sombras. *Arch Bronconeumol*. 2009; 45(Supl1): 25-9.
688. Boulet LP, FitzGerald MJ, Levy ML, Cruz AA, Pedersen S, Haahtela T et al. A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care. *Eur Respir J*. 2012; 39: 1220-29.
689. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? *J Contin Educ Health Prof*. 2006; 26: 13-24.