Pneumococcal acute otitis media aom biology essay

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Q1 Please confirm that given names and surnames have been identified correctly. Q2 Please provide an e-mail address for correspondence purposes. Please check this box or indicate your approval ifyou have no corrections to make to the PDF fileThank you for your assistance. 12 Pneumococcal acute otitis media in infants and children in central3 Romania, 2009–2011: microbiological characteristics and potential4 coverage by pneumococcal conjugate vaccines5 O. Falup-Pecurariu Q1a, E. Leibovitz b,*, A. Mercas a, L. Bleotu a, C. Zavarache a, N. Porat b, 6 R. Dagan b, D. Greenberg b7 a Department of Pediatrics, Children’s Hospital, Faculty of Medicine, Transilvania University, Brasov, Romania8 b Pediatric Infectious Disease Unit,

Soroka University Medical Center, Ben-Gurion University, Beer-Sheva, Israel Q291011 1. Introduction12 Acute otitis media (AOM) is the most frequent bacterial disease13 of childhood, affecting millions of children worldwide and14 remaining a major public health problem. 1–3 The most common15 causative agents in AOM are Streptococcus pneumoniae, non-16 typeable Haemophilus influenzae (NTHi), Moraxella catarrhalis, and17 Streptococcus pyogenes. 4–8 Together, S. pneumoniae and NTHi18 account for 60–80% of the AOM pathogens. 9 Antibiotic resistance19 is high in pneumococcal AOM, with penicillin- and amoxicillin-20 non-susceptible strains accounting for 30–70% of cases. 10–16 The21 most commonly encountered S. pneumoniae serotypes in AOM are22 6A, 6B, 14, 19A, 19F, and 23F. 15, 16 The highest antibiotic non-23 susceptibility is found in vaccine serotypes 6A, 6B, 9 V, 14, 19A, 24 19F, and 23F. 11, 12, 15, 1625 Information on antibiotic resistance patterns and serotype26 distribution of S. pneumoniae isolates in infants and young children27 in Romania is limited. In a multinational study, 42% of28 S. pneumoniae AOM isolates from Romania were intermediately29 or fully resistant to penicillin. 17 In three studies investigating30 pneumococcal mucosal and invasive disease isolates inInternational Journal of Infectious Diseases xxx (2013) xxx. e1–xxx. 5A R T I C L E I N F OArticle history: Received 23 November 2012Received in revised form 26 December 2012Accepted 2 February 2013Corresponding Editor: Eskild Petersen, Aarhus, DenmarkKeywords: Acute otitis mediaStreptococcus pneumoniaeAntibiotic resistanceChildrenS U M M A R YObjective: To assess the epidemiological and microbiological characteristics of pneumococcal acute otitismedia (AOM) in children in Brasov, Central Romania, before the

introduction of pneumococcal conjugatevaccine (PCV) into the routine national immunization program. Methods: All AOM patients aged <5 years who underwent tympanocentesis or presented with purulentotorrhea of _24 h duration during 2009–2011 were enrolled. Results: Two hundred and twelve consecutive AOM patients had a middle ear fluid (MEF) cultureperformed; 99 (46. 6%) episodes occurred in patients <12 months of age. One hundred and eleven (52. 4%)episodes were culture-positive. Tympanocentesis was performed in 142 patients and spontaneousotorrhea cultures in 70 patients. Overall, 114 pathogens were recovered: Streptococcus pneumoniae wasthe most common isolate (81 isolates, 70. 3% of all culture-positive episodes), followed by non-typeableHaemophilus influenzae (26, 20. 7%), Streptococcus pyogenes (5, 4. 5%), and Moraxella catarrhalis (2, 1. 8%). Antibiotic susceptibility and serotyping were performed for 48 (59. 3%) S. pneumoniae isolates: 45 (93. 8%)were non-susceptible to penicillin (minimal inhibitory concentration (MIC) _2. 0 mg/ml in 24, 53. 3%) and37 (77. 1%) isolates had ceftriaxone MIC values _0. 5 mg/ml (16 with MIC > 2. 0 mg/ml). S. pneumoniaenon-susceptibility rates to trimethoprim–sulfamethoxazole, erythromycin, and clindamycin were75. 0%, 58. 3%, and 35. 4%, respectively. All isolates were susceptible to chloramphenicol. Multidrugresistance was found in 33 (68. 7%) isolates. The most common S. pneumoniae serotypes were 19F (14, 29. 2%), 6B (8, 16. 7%), 23F (8, 16. 7%), and 14 (6, 12. 5%). Serotype 19A was found in three (6. 2%) patientsand 6A in two (4. 1%). Non-PCV13 serotypes represented six (12. 6%) of all serotypes (four of them nonsusceptibleto penicillin). Thirty-six (75. 0%) isolates were potentially covered by PCV7, 37 (77. 0%) byPCV10,

and 42 (87. 5%) by PCV13. Conclusions: (1) S. pneumoniae was the most prevalent pathogen, with frequent antibiotic resistance andmulti-resistance patterns; (2) most pneumococcal AOM and multidrug-resistant episodes could beprevented by PCVs. _ 2013 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.* Corresponding author. G ModelIJID 1656 1–5Please cite this article in press as: Falup-Pecurariu O, et al. Pneumococcal acute otitis media in infants and children in central Romania, 2009–2011: microbiological characteristics and potential coverage by pneumococcal conjugate vaccines. Int J Infect Dis (2013), http://dx. doi. org/10. 1016/j. ijid. 2013. 02. 002Contents lists available at SciVerse ScienceDirectInternational Journal of Infectious Diseasesjou r nal h o mep ag e: w ww . elsevier . co m /loc ate/ijid1201-9712/$36. 00 – see front matter _ 2013 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. http://dx. doi. org/10. 1016/j. ijid. 2013. 02. 00231 HIV-negative and HIV-positive infants and children in northeast-32 ern Romania, high rates of recovery of serotypes 19A and 23F and33 of multidrug-resistant (MDR) organisms were reported. 18–2034 Recently, high rates of colonization with S. pneumoniae (reaching35 71% in children 13–24 months of age) accompanied by high36 resistance rates to most of the commonly used antibiotic drugs37 were reported among healthy and sick infants and children38 <5 years old in central Romania. 2139 Active and continuous surveillance of the microbiology and40 antibiotic susceptibility patterns of AOM pathogens in Romania is41 important, particularly during the period preceding the introduc-42 tion of pneumococcal conjugate vaccine (PCV). The aims of the43 present study were to assess: (1) the overall distribution

of44 otopathogens and their antibiotic resistance patterns; and (2) PCV45 coverage of S. pneumoniae middle ear fluid (MEF) isolates in Brasov, 46 central Romania, during 2009–2011. 47 2. Patients and methods48 We conducted a prospective epidemiological study between49 January 1, 2009 and December 31, 2011, at the Children's Hospital50 of Brasov, in the central part of Romania. Brasov has a population of51 400 000 inhabitants and the hospital is the only medical center52 providing medical care for infants and children in the city. The53 study protocol was approved by the institutional review board of54 the University of Transilvania, Brasov. Informed consent was55 obtained from the legal guardians of all children. 56 2. 1. Patients and procedures57 The study patients were infants and children aged <5 years58 diagnosed with AOM by a pediatrician, family physician, or59 otolaryngologist. The diagnosis was done when the patients60 presented with: (1) symptoms and physical findings consistent61 with AOM (fever, irritability, tugging of the ear, and redness and62 bulging of the tympanic membrane with blurring of its anatomic63 landmarks); (2) acute illness lasting _7 days. Bulging of the64 tympanic membrane (in addition to clinical symptoms of AOM)65 was present in all cases where a tympanocentesis was performed. 66 Culture specimens were obtained by either tympanocentesis or67 collection of pus from draining the ears (if lasting _24 h before68 enrollment). Patients with tympanostomy tubes were excluded69 from the study. In all episodes, we collected information on the70 patient's age, sex, and ethnicity, the type of specimen (tympano-71 centesis or draining pus), and the patient's AOM history and recent72 antibiotic treatment. Data were obtained from the medical records73 of the

hospital, clinical medical chart, or parent interview. None of74 the patients had been immunized with a PCV before enrollment. 75 Tympanocentesis was performed by the study otolaryngologist76 (AM) as previously described. 7, 1277 2. 2. Bacteriology78 Swabs of MEF aspirates were placed in MW173 Amies transport79 medium (Transwab; Medical Wire and Equipment), plated80 immediately on trypticase agar containing 5% sheep blood and81 5 mg/ml gentamicin, and on chocolate agar, and incubated at 35 8C82 for 48 h in a 5% enriched CO2 atmosphere. Identification, 83 serotyping, and testing of antimicrobial susceptibility to penicillin84 and ceftriaxone (by E-test, PDM Epsilometer, AB Biodisk, Solna, 85 Sweden) and erythromycin, clindamycin, chloramphenicol, and86 trimethoprim–sulfamethoxazole (TMP–SMX) (by disk diffusion)87 were performed as described elsewhere, in accordance with the88 Clinical and Laboratory Standards Institute (CLSI) recommenda-89 tions. 22 Non-susceptibility to _3 antibiotic classes was considered90 multidrug resistance (MDR). Serotyping was done by quellung91 reaction. 23 The organisms were sub-cultured and stored at _70 8C92 at the Microbiology Laboratory of the Children' Hospital of Brasov93 and were further transported by air to the Pediatric Infectious94 Disease Unit Laboratory of the Soroka University Medical Center, 95 Beer-Sheva, Israel, where all antimicrobial susceptibility testing96 and serotyping was carried out. 97 S. pneumoniae isolates were considered susceptible to penicillin98 if the minimal inhibitory concentration (MIC) values were99 _0. 06 mg/ml, intermediate if penicillin MIC values were between100 0. 125 mg/ml and 1. 0 mg/ml, and resistant if MIC values were101 _2. 0 mg/ml. Ceftriaxone intermediate resistance was defined by102 MICs values between 0. 5 and 1.

0 mg/ml, and high resistance by103 MICs values > 2. 0 mg/ml. 104 2. 3. Statistical analysis105 Data were recorded using Microsoft Access office software. The106 statistical analysis was performed using SPSS 17. 0 software. 107 Contingency table analysis for comparing rates between un-108 matched samples was performed using the Chi-square test or109 Fisher's exact test, as appropriate. The Student independent110 samples t-test was used to compare continuous variables. The111 percentages of serotype coverage were calculated and compared112 between PCV7 (serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F), PCV10113 (PCV7 plus serotypes 1, 5, and 7F), and PCV13 (PCV10 plus114 additional serotypes 3, 6A, and 19A). All tests were considered115 significant if p-values were <0. 05. 116 3. Results117 During the study period, 212 consecutive infants and young118 children <5 years of age were enrolled. There were 120 (56. 6%)119 males. The mean age (_ standard deviation) was 18. 0 _ 14. 2 months. 120 Ninety-nine (46. 6%) episodes occurred in patients <12 months old121 and 136 (64. 2%) episodes occurred in children <2 years old. One122 hundred and eleven samples (52. 4%) were culture-positive. Children123 with culture-positive MEF were older than children with culture-124 negative MEF (20. 6 _ 15. 2 months vs. 15. 4 _ 12. 6 months, p = 0. 008). 125 Tympanocentesis was recorded in 142 patients and spontane-126 ous otorrhea in 70 patients. No differences were recorded in the127 proportions of spontaneous perforation between children with128 culture-positive and children with culture-negative MEF (38/111, 129 34. 2% vs. 32/101, 31. 7%, p = 0. 7). 130 A total of 114 isolates (76 from tympanocentesis and 38 from131 spontaneous otorrhea specimens) were recovered. S.

pneumoniae132 was the most common isolate (81 isolates, 78 episodes, 71. 1% of all133 pathogens recovered and 70. 3% of all culture-positive episodes), 134 followed by NTHi (26, 23; 22. 8% and 20. 7%), Streptococcus135 pyogenes (5, 5; 4. 4% and 4. 5%) and Moraxella catarrhalis (2, 2; 136 1. 8% and 1. 8%) (Table 1). In three patients (1. 4% of all episodes), 137 both S. pneumoniae and NTHi were isolated. No differences were138 recorded in the percentages of S. pneumoniae recovered fromTable 1Acute otitis media microbiology of 212 episodes (111 culture-positive) during2009–2011Pathogen No. of episodesaStreptococcus pneumoniae 78 (70. 3)Haemophilus influenzae 23 (20. 7)Streptococcus pyogenes 5 (4. 5)Moraxella catarrhalis 2 (1. 8)S. pneumoniae + H. influenzae 3 (2. 7)Culture-positive 111Culture-negative 101Total 212a The percentage of all culture-positive episodes is given in parenthesis. O. Falup-Pecurariu et al. / International Journal of Infectious Diseases xxx (2013) xxx. e1–xxx. e5 e2G ModelIJID 1656 1–5Please cite this article in press as: Falup-Pecurariu O, et al. Pneumococcal acute otitis media in infants and children in central Romania, 2009–2011: microbiological characteristics and potential coverage by pneumococcal conjugate vaccines. Int J Infect Dis (2013), http://dx. doi. org/10. 1016/j. ijid. 2013. 02. 002139 tympanocentesis compared with those isolated from spontane-140 ous otorrhea (55/76, 72. 4% vs. 26/38, 68. 4%, p = 0. 7). No141 differences were recorded in the mean age at diagnosis of142 patients with S. pneumoniae AOM compared with patients with143 AOM caused by other etiologic agents (18. 16 _ 7. 08 vs. 144 24. 59 _ 18. 37 months, p = 0. 1). 145 Reliable information on prior antibiotic treatment (during the146 24 h preceding AOM diagnosis) was available for 68/111 (60.

2%)147 culture-positive patients; 29/68 (42. 6%) culture-positive patients148 received previous antibiotic treatment compared with 34/101149 (33. 7%) culture-negative patients (p = 0. 24). The representation of150 S. pneumoniae was higher in patients previously untreated with151 antibiotics compared with patients treated with antibiotics (28/39, 152 71. 7% vs. 14/29, 48. 3%, p = 0. 03). 153 Antibiotic susceptibility testing and serotyping were performed154 for 48/81 (59. 3%) S. pneumoniae isolates. Forty-five (93. 8%)155 S. pneumoniae isolates were non-susceptible to penicillin; 24156 (53. 3%) had MIC values _2. 0 mg/ml. Six isolates had a penicillin157 MIC value of 16. 0 mg/ml, one had a MIC of 8. 0 mg/ml, and three had158 a MIC of 4. 0 mg/ml. Thirty-seven (77. 1%) isolates had ceftriaxone159 MIC values _0. 5 mg/ml (32. 0 mg/ml for five isolates, 4. 0 mg/ml for160 nine isolates, 2. 0 mg/ml for one isolate, and 1. 0 mg/ml for one161 isolate). The non-susceptibility rates to TMP–SMX, erythromycin, 162 and clindamycin were 36/48 (75%), 28/48 (58. 3%), and 17/48163 (35. 4%), respectively. All isolates were susceptible to chloram-164 phenicol. Resistance to _1 antibiotic class was found in 44 (91. 7%)165 and MDR in 33 (68. 7%) S. pneumoniae isolates. No differences were166 recorded in the resistance patterns to antibiotics of S. pneumoniae167 recovered from tympanocentesis versus the isolates recovered168 from culture of spontaneous otorrhea. 169 The most common S. pneumoniae serotypes were: 19F (14, 170 29. 2%), 6B (8, 16. 7%), 23F (8, 16. 7%), and 14 (6, 12. 5%) (Table 2). 171 Serotype 19A was found in three (6. 2%) patients and 6A in two (4. 1%)172 patients. The non-PCV13 serotypes represented six (12. 6%) of all173 serotypes, and four of them were non-susceptible to penicillin. Six174 (75%) of the eight serotype

23F isolates had a penicillin MIC of175 16. 0 mg/ml and a ceftriaxone MIC value of 32. 0 mg/ml; 3/14 (21. 4%)176 serotype 19F isolates had a penicillin MIC value of 4. 0 mg/ml and one177 had a penicillin MIC value of 8. 0 mg/ml. The MDR isolates included, 178 in descending order, serotypes 19F, 6B, 23F, 19A, and 6A. Of the 14179 serotype 19F isolates, 13 (92. 9%) were non-susceptible to penicillin, 180 erythromycin, and TMP–SMX, and 9/13 (69. 1%) also to clindamycin. 181 All eight serotype 6B isolates were non-susceptible to penicillin, 182 erythromycin, TMP–SMX, and clindamycin. All eight serotype 23F183 isolates were non-susceptible to penicillin, erythromycin, and TMP–184 SMX, and 5/8 (62. 5%) also to clindamycin. All three serotype 19A185 isolates were non-susceptible to penicillin, erythromycin, and TMP–186 SMX, and 2/3 (66. 7%) also to clindamycin. One of the two serotype 6A187 isolates was non-susceptible to penicillin, erythromycin, TMP–SMX, 188 and clindamycin. 189 Of the 48 tested S. pneumoniae serotype isolates, 36 (75. 0%)190 are included in PCV7, 37 (77. 0%) in PCV10, and 42 (87. 5%) in191 PCV13. 192 4. Discussion193 The present study aimed to provide baseline data on the194 contribution of S. pneumoniae to the etiology of AOM in Romania. 195 We also analyzed the resistance patterns to antibiotics and the196 serotype distribution of this pathogen before the introduction of197 universal PCV immunization in Romania. 198 Our main findings were: (1) infants and young children with199 culture-positive AOM were older compared with those with200 culture-negative AOM; (2) S. pneumoniae was the dominant201 etiologic agent, being isolated in 74. 3% of the culture-positive202 patients; (3) most of the isolates were resistant to penicillin, 203 erythromycin, and TMP–SMX, and MDR was very common; 204 (4) the

current PCVs could potentially prevent most of the205 pneumococcal AOM in the region. The present study may206 provide a basis for follow-up and monitoring of AOM etiology207 and resistance patterns after the introduction of PCV into the208 national program. 209 In the Brasov area, we recently reported that of 205210 pneumococcal nasopharyngeal isolates obtained from infants211 and children <5 years of age (attending daycare centers, 212 immunization clinics, or visiting the pediatric emergency room213 of the hospital for different acute illnesses, as well as healthy214 patients admitted to the surgery department for elective215 procedures), 83% were non-susceptible to penicillin and 18%216 were non-susceptible to ceftriaxone, of which 40. 5% and 16% were217 highly-resistant to penicillin and ceftriaxone, respectively. 21 The218 non-susceptibility rates to erythromycin, TMP–SMX, tetracycline, 219 and clindamycin were also high (> 50% for each antibiotic) and220 MDR was found in 67% of isolates. The most common pneumo-221 coccal serotypes isolated were 23F, 6B, 19F, 14, 6A, and 19A, and222 the potential coverage by PCV7, PCV10, and PCV13 was 66%, 74%, 223 and 80%, respectively. This is consistent with the AOM findings in224 the current study. 225 The major limitation of this study derives from the small226 number of pneumococcal isolates evaluable for antibiotic227 susceptibility testing and serotyping. On the other hand, the data228 presented here from MEF cultures performed in AOM patients229 diagnosed and treated at the Brasov Children’s Hospital are230 additional to previously published information on the pneumo-231 coccal carriage in patients enrolled from daycare centers and232 immunization clinics in the city of Brasov and also from the233 emergency room and surgery department of the hospital (which

is234 the only referral pediatric hospital in the whole area and is the235 only site where MEF and nasopharyngeal cultures are per-236 formed). 21 Therefore, we are convinced that these two studies237 from Brasov provide an up-to-date and reliable picture of the local238 pneumococcal burden in infants and young children and the239 antibiotic susceptibility, serotype distribution, and potential240 serotype coverage by PCVs in the city of Brasov and the241 surrounding areas. At the present time, additional limited data242 from nasopharyngeal and MEF pneumococcal isolates obtained243 from infants and young children are available from the244 northeastern (Iasi) and southern (Bucharest) areas of the country245 and provide a similar picture in terms of colonization burden, 246 extremely high antibiotic resistance rates, serotype distribution, 247 and potential PCV coverage. 17–21, 24248 The presented data, together with the additional data from249 northeastern Romania, raise major concerns regarding the250 unskilled used of antibiotics in this country, leading to highTable 2Streptococcus pneumoniae serotype distribution (in decreasing frequency) for 48acute otitis media episodesSerotype No. episodes (%) MDR19F 14 (29. 2) 13 (92. 9%)23F 8 (16. 7) 8 (100%)6B 8 (16. 7) 8 (100%)14 6 (12. 5) -19A 3 (6. 2) 3 (100%)6A 2 (4. 1) 1 (50%)22F 2 (4. 1) -9V 1 (2. 1) -34 1 (2. 1) -9A 1 (2. 1) -7F 1 (2. 1) -Omni-negative 1 (2. 1) -Total 48 33 (68. 7%)MDR, multiple drug resistance. O. Falup-Pecurariu et al. / International Journal of Infectious Diseases xxx (2013) xxx. e1–xxx. e5 e3G ModelIJID 1656 1–5Please cite this article in press as: Falup-Pecurariu O, et al. Pneumococcal acute otitis media in infants and children in central Romania, 2009–2011: microbiological characteristics and potential coverage by pneumococcal conjugate vaccines.

Int J Infect Dis (2013), http://dx. doi. org/10. 1016/j. ijid. 2013. 02. 002resistance. Furthermore, the high rate of resistance is of concern in252 terms of the efficacy of current antimicrobial agents in the253 treatment of AOM. 254 Faced with the alarming resistance data presented in this255 study, an intervention program including a major reduction in256 antibiotic use, combined with introduction of routine vaccination257 with PCVs, is much needed in Romania. In France, Cohen et al. 25258 clearly showed that the implementation of a national program of259 reduction of inappropriate antibiotic use markedly contributed to260 the efficacy of PCV7 in reducing the carriage of penicillin-non-261 susceptible pneumococci in children with AOM. In a study262 evaluating the association between antibiotic use in the commu-263 nity and the increase in antibiotic-resistant S. pneumoniae264 carriage in Bedouin children aged <5 years in southern Israel265 from 1998 to 2005, Greenberg et al. 26 examined all the antibiotic266 prescriptions provided from two community primary pediatric267 clinics and reported a decrease by 19% in the total annual268 prescription rates, mainly as a result of a reduction in amoxicillin–269 clavulanate prescriptions. Oral cephalosporins, erythromycin, 270 and penicillin prescription rates decreased significantly as well, 271 but azithromycin prescription rates increased significantly during272 the study period. In parallel, the authors analyzed the273 S. pneumoniae nasopharyngeal carriage in healthy children274 <5 years old from the same communities and were able to275 demonstrate an increase in the proportion of nasopharyngeal276 S. pneumoniae with penicillin MICs _1. 0 mg/ml from 8% to 21% and277 significant increases in resistance to clindamycin, erythromycin, 278 and

tetracycline and also in multidrug resistance. The authors279 suggested an association between the increased carriage of MDR280 S. pneumoniae and the increased azithromycin consumption, and281 cautioned that a reduction in the total antibiotic use may not be282 sufficient as long as antibiotics with a high potential for the283 promotion of multidrug resistance, like azithromycin, continue to284 be used widely. 26285 The introduction of the 7-valent conjugate PCV (PCV7)286 had a major role in the reduction of invasive and mucosal287 disease rates caused by S. pneumoniae and of the antimicrobial288 resistance of the isolated organisms, and also, although less289 impressive, in the reduction of nasopharyngeal colonization290 and AOM cases caused by this pathogen. 27–32 In our study, the291 good coverage of overall pneumococcal serotypes and also of292 MDR pneumococcal isolates by all PCVs, and in particular by293 PCV13 (87. 5% and 100%, respectively), are important and294 encouraging findings. 295 PCV7 was registered in Romania in September 2007, but is not296 yet included in the routine immunization program for Romanian297 infants and children. Initiation of a national immunization298 program is urgently needed in order to achieve a reduction in299 pneumococcal disease in general and of antibiotic-resistant and300 MDR pneumococcal AOM in particular. 301 Acknowledgements302 This study was supported by a European Society of Infectious303 Diseases (ESPID) Research Grant (2010). 304 Conflict of interest: Prof. Ron Dagan has received grants/research305 support from Berna/Crucell, Pfizer, MSD, and Protea; has been a306 scientific consultant for GlaxoSmithKline, Pfizer, NASVAX, and307 MSD and a speaker

for Berna/Crucell, GlaxoSmithKline, and Pfizer; 308 he is a shareholder in Protea/NASVAX. All other authors report no309 conflict of interest.