

Use of Palivizumab in Infants and Young Children With Severe Respiratory Disease: A Delphi Study

Mirella Gaboli, MD, PhD,^{1*} Òscar Asensio de la Cruz, MD,²
 María Isabel Barrio Gómez de Agüero, MD, PhD,³ Antonio Moreno-Galdó, MD, PhD,⁴
 Guadalupe Pérez Pérez, MD, PhD,⁵ and Manuel Sánchez-Solís de Querol, MD, PhD⁶

Summary. Objective: To achieve a consensus of opinion among an expert group of pediatric pulmonologists regarding the appropriateness of the off-label use of palivizumab for some pediatric patients with severe respiratory diseases. Methods: A two-round modified Delphi technique was used. A 43-item self-administered questionnaire grouped into seven clinical scenarios was developed. Level of agreement for each statement was ranked on a 0–9 scale with 0 being total disagreement and 9 total agreement. Consensus was sought through the feedback of information and iteration. The final responses were evaluated for median and interquartile range to determine which questions the group had reached consensus about, either affirmatively or negatively. Results: Consensus was obtained for 24/43 statements (55.81%), including use of palivizumab for prevention of respiratory syncytial virus (RSV) infection in children with severe respiratory involvement due to neuromuscular disease, congenital or acquired immunodeficiency, storage disease, cystic fibrosis, diseases involving impaired ciliary clearance, patients operated on esophageal atresia and/or tracheoesophageal fistula, diaphragmatic hernia, bronchopulmonary malformations, severe tracheomalacia, lung transplant recipients and patients in the waiting list for lung transplant, patients oxygen-dependent for severe interstitial pulmonary disease and patients with severe pulmonary hypertension. Consensus against the use of palivizumab as prevention of RSV infection was also achieved in almost all the recurrent wheezing/asthma attacks situations. Conclusion: A set of indication for off-label uses of palivizumab in pediatric pulmonology was developed in accordance with the degree of professional consensus on which they were based. The applicability of the present results to clinical practice should be evaluated individually and reviewed periodically in the light of new emerging evidence. Further studies are needed to add evidence to the most frequent and clinically oriented scenarios that have shown higher levels of uncertainty. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

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¹Pediatric Pulmonology and Pediatric Intensive Care Units, Department of Pediatrics, Hospital Universitario de Salamanca and University of Salamanca, Salamanca, Spain.

²Pediatric Pulmonology and Cystic Fibrosis Unit, Service of Pediatrics, Hospital de Sabadell, Corporació Sanitària Parc Taulí, Sabadell, Universitat Autònoma de Barcelona, Barcelona, Spain.

³Pediatric Pulmonology Unit, Service of Pediatrics, Hospital Universitario La Paz, Madrid, Spain.

⁴Pediatric Pulmonology and Cystic Fibrosis Unit, Hospital Universitari Vall d'Hebron, Departament de Pediatria, Obstetrícia i Ginecologia i Medicina Preventiva, Universitat Autònoma de Barcelona, Barcelona, Spain.

⁵Pediatric Pulmonology Unit, Service of Pediatrics, Hospital Universitario Virgen Macarena, Sevilla, Spain.

⁶Pediatric Pulmonology Unit, Service of Pediatrics, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain.

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*Correspondence to: M. Gaboli, MD, PhD, Department of Pediatrics, Hospital Universitario de Salamanca, Paseo San Vicente 58-182, E-37007 Salamanca, Spain. E-mail: mgaboli@usal.es, mgaboli@hotmail.com

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INTRODUCTION

Prevention remains the most effective approach against severe respiratory syncytial virus (RSV) infection in infants and young children.¹ Patients with severe respiratory disease, particularly in the presence of chronic respiratory insufficiency, constitute a risk group for the development of life-threatening RSV infection.^{2–6} The significant morbidity and mortality in groups at risk and the limited therapeutic options together with recent advances in the knowledge of the relationship between RSV infection and host factors, reinforces the interest in epidemiological aspects and care of the patients, in order to reduce the incidence and severity of these infections. However, clinicians' perception of the magnitude of the problem may be different according to their knowledge, professional field, characteristics of the patients attended, and clinical experience, which may account for the variability among professionals providing care to the same type of patients in daily practice.

In addition to basic hygienic measures, intramuscular immunoprophylaxis with palivizumab, a humanized murine monoclonal antibody produced by recombinant technology and directed against the surface RSV fusion protein, has been shown to be cost-effective in the prevention of acute infection in high-risk infants and in the reduction of RSV hospitalizations.^{7–9} Although the pharmacotherapeutic profile of licensed indications of palivizumab are well defined, especially prematurity, chronic lung disease in infants born preterm and/or hemodynamically significant congenital heart disease, there is some heterogeneity for the use of this drug in patients with severe respiratory conditions excluded by indication from clinical trials.^{10,11} Therefore, the use of palivizumab in some specific indications and the cost–and risk–benefit relationships are still a matter of debate and should be assessed according to the best available evidence, cumulative clinical experience, and direct knowledge of the outcome of children affected by the specialists in charge.

This study aimed to achieve a consensus of opinion among an expert group of pediatric pulmonologists regarding the adequacy of the off-label use of palivizumab for some pediatric patients with severe respiratory diseases using the Delphi method. The Delphi technique is a well-established consensus method to gather and refine expert opinion on any given issue and has been previously used in different pediatric studies.^{10–16}

METHODS

Design and Organization of the Study

A two-round modified Delphi technique was used to reach agreement among members of the Spanish Society of Pediatric Pulmonology with recognized experience in

pediatric respiratory diseases throughout Spain, about the pertinence of off-label indications of palivizumab for the treatment of some infants with severe respiratory diseases.

The modified Delphi method is a technique to arrive at a group consensus regarding an issue under investigation that was originally developed at the RAND Corporation in the 1950s.¹⁷ It is a structured and multistage process where a panel of experts are invited to take part in a series of rounds to identify, clarify, and finally reach a consensus for a subject matter in which precise information is lacking. The method relies on soliciting anonymous individual answers to written questions by survey. Consensus is sought through the feedback of information and iteration. The final responses are evaluated for interquartile range (IQR) and medians, variance and means to determine which questions the group has reached consensus about, either affirmatively or negatively. To avoid the potential influence of the chairperson (in the choice of the expert panel and discussion of results), a multicenter research group of different origin and interest has planned and co-directed the present study; this research group also followed systematized and objective procedures in the selection of panelists, statistical analysis, and interpretation of results.^{18,19}

The study was conducted in four phases: (1) formation of the scientific committee composed of six persons and selection of an external methodological expert for review of the literature and construction of the questionnaire statements (professional criteria and clinical recommendations subjected to debate); (2) establishment of an expert panel of all accredited members of the Spanish Society of Pediatric Pulmonology, who after receiving an invitation letter describing the project, agreed to participate in the survey; (3) development of an electronic structured questionnaire for web-based data collection; and (4) collection of data, analysis of final results, and discussion of findings by the scientific committee in a face-to-face meeting.

Development of the Questionnaire

A 43-item self-administered questionnaire grouped into seven clinical scenarios was developed by members of the scientific committee after a normalized systematic review of the literature²⁰ in the MEDLINE, EMBASE, and IME (*Índice Médico Español*, Spanish Medical Index) databases (until December 2011). References of the articles retrieved were also scrutinized for potentially relevant studies.

The preliminary list of proposed items underwent a process of revision, selection, and adaptation by the scientific committee to reach a definite version approved unanimously by all members. As shown in Table 1, the six clinical scenarios referred to patients with significant

TABLE 1—Consensus Achieved by Experts After Two Delphi Rounds: Panelists (%) Found in the Three-Point Region of the Median

According to the available evidence, your clinical experience, and personal knowledge, do you think that palivizumab may be indicated for the prophylaxis of respiratory syncytial virus (RSV) infection in the following clinical scenarios?	Median (IQR)	Mean score	Panelists in the three-point region of the median (%) ¹
Neuromuscular diseases			
1. Patients with severe central neurological conditions (hydrocephalus, central apneas, cerebral palsy, etc.) until 12 months of age at the onset of the RSV epidemic season ²	7 (3)	5.94	57.1
2. Patients with severe central neurological conditions (hydrocephalus, central apneas, cerebral palsy, etc.) until 24 months of age at the onset of the RSV epidemic season ³	5 (4)	4.79	14.7
3. Patients with neuromuscular disease until 12 months of age at the onset of the RSV epidemic season	7 (1)	6.88	79.4
4. Patients with neuromuscular disease until 24 months of age at the onset of the RSV epidemic season ²	7 (4)	6.03	54.5
5. Patients with neuromuscular disease with marked hypotonia until 12 months of age at the onset of the RSV epidemic season	8 (2)	7.43	86.4
6. Patients with neuromuscular disease with marked hypotonia until 24 months of age at the onset of the RSV epidemic season	7 (1)	7.17	86.1
Underlying systemic disease			
7. Patients with polymalformative syndrome, without heart disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season ²	7 (3)	5.77	51.4
8. Patients with polymalformative syndrome, without heart disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season ³	6 (4)	5.08	22.2
9. Patients with chromosomal anomaly, without heart disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season ²	7 (3)	5.80	54.3
10. Patients with chromosomal anomaly, without heart disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season ³	5 (2)	4.43	48.5
11. Patients with congenital or acquired immunodeficiency, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season	7 (2)	7.37	82.9
12. Patients with storage disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season	7 (0)	6.62	79.4
13. Patients with storage disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season ³	6 (4)	5.51	28.6
Cystic fibrosis and other diseases with impaired ciliary clearance			
14. Patients diagnosed of cystic fibrosis until 24 months of age at the onset of the RSV epidemic season	8 (2)	7.44	86.0
15. Patients diagnosed of cystic fibrosis who had not presented clinical symptoms compatible with RSV infection until 4 years of age at the onset of the RSV epidemic season	3 (1)	3.39	69.4
16. In patients with severe disease and carriers of chronic infection with <i>Pseudomonas aeruginosa</i> prophylaxis should be extended up to 4 years of age at the onset of the RSV epidemic season ³	5 (4)	4.89	17.1
17. Patients with diseases involving impaired ciliary clearance (ciliary dyskinesia, bronchiectasis unrelated to cystic fibrosis, etc.) until 12 months of age at the onset of the RSV epidemic season	7 (4)	6.78	68.3
18. Patients with diseases involving impaired ciliary clearance (ciliary dyskinesia, bronchiectasis unrelated to cystic fibrosis, etc.) until 24 months of age at the onset of the RSV epidemic season ²	7 (6)	6.39	63.9
Congenital malformations of the lung and tracheobronchial tree			
19. Patients operated on for esophageal atresia and/or tracheoesophageal fistula until 12 months of age at the onset of the RSV epidemic season	7 (3)	6.72	72.1

(Continued)

Table 1—(Continued)

According to the available evidence, your clinical experience, and personal knowledge, do you think that palivizumab may be indicated for the prophylaxis of respiratory syncytial virus (RSV) infection in the following clinical scenarios?	Median (IQR)	Mean score	Panelists in the three-point region of the median (%) ¹
20. Patients operated on for esophageal atresia and/or tracheoesophageal fistula until 24 months of age at the onset of the RSV epidemic season ²	7 (5)	5.94	51.4
21. Patients with severe tracheomalacia until 12 months of age at the onset of the RSV epidemic season	7 (1)	7.05	78.6
22. Patients with severe tracheomalacia until 24 months of age at the onset of the RSV epidemic season ²	7 (4)	6.71	65.7
23. Patients with chronic respiratory insufficiency who were operated on for severe congenital diaphragmatic hernia in the neonatal period until 12 months of age at the onset of the RSV epidemic season	8 (2)	7.43	85.7
24. Patients with chronic respiratory insufficiency who were operated on for severe congenital diaphragmatic hernia in the neonatal period until 24 months of age at the onset of the RSV epidemic season	7 (3)	6.77	67.4
25. Patients with bronchopulmonary malformation and respiratory symptoms until 12 months of age at the onset of the RSV epidemic season	7 (2)	6.65	72.1
26. Patients with bronchopulmonary malformation and respiratory symptoms until 24 months of age at the onset of the RSV epidemic season	7 (3)	6.44	66.7
Lung transplantation and severe pulmonary diseases			
27. Lung transplant recipients until 24 months of age at the onset of the RSV epidemic season	8 (2)	7.69	83.3
28. Lung transplant recipients until 4 years of age at the onset of the RSV epidemic season ³	6 (2)	5.94	44.4
29. Patients in the waiting list for lung transplantation under 2 years of age at the onset of the RSV epidemic season	8 (2)	7.64	83.3
30. Patients in the waiting list for lung transplantation under 4 years of age at the onset of the RSV epidemic season ²	7 (2)	6.28	58.3
31. Patients with oxygen-dependent severe interstitial pulmonary disease or bronchiolitis obliterans under 2 years of age at the onset of the RSV epidemic season	8 (2)	7.85	92.7
32. Patients with idiopathic pulmonary hypertension under 2 years of age at the onset of the RSV epidemic season	8 (2)	7.71	85.7
33. Patients with idiopathic pulmonary hypertension under 4 years of age at the onset of the RSV epidemic season ²	3 (2)	4.08	58.3
Asthma/recurrent wheezing			
34. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, at risk of recurrent wheeze based on assessment with the asthma predictive index (API)	3 (2)	2.67	83.3
35. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season	3 (3)	2.98	72.1
36. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, without family history of atopy	3 (3)	3.28	72.1
37. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, with family history of atopy	3 (2)	2.79	85.3
38. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, and positive API	3 (2)	3.12	67.4
39. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, and negative API ²	3 (2)	3.57	62.9

(Continued)

Table 1—(Continued)

According to the available evidence, your clinical experience, and personal knowledge, do you think that palivizumab may be indicated for the prophylaxis of respiratory syncytial virus (RSV) infection in the following clinical scenarios?	Median (IQR)	Mean score	Panelists in the three-point region of the median (%) ¹
Intravenous administration			
40. Patients with indication of prophylaxis in which prophylaxis was not correctly administered, with confirmed RSV infection and severe clinical condition as treatment of RSV, until 12 months of age at the onset of the RSV epidemic season ³	5 (2)	4.97	61.8
41. Patients with indication of prophylaxis in which prophylaxis was not correctly administered, with confirmed RSV infection and severe clinical condition as treatment of RSV, until 24 months of age at the onset of the RSV epidemic season ³	5 (1)	4.59	64.8
42. Patients with established indication of prophylaxis in which the use of the intramuscular route is contraindicated	7 (1)	6.91	92.9
43. Patients with severe underlying disease in which prophylaxis is not indicated, as treatment of severe RSV infection ³	5 (2)	4.61	66.6

IQR, interquartile range.

¹Percentage of panelists scoring in the three-point range ([1–3], [4–6], [7–9]) that included the median value.

²Item in which consensus was not reached as >33% of the panelists scored outside of the three-point range that included the median value.

³Item in which consensus was not reached because of “indeterminate” level of group consensus.

respiratory involvement and a section related to the intravenous administration of palivizumab, each of them including a variable number of items, as follows: “neuromuscular diseases” (six items), “underlying systemic disease” (seven items), “cystic fibrosis and other diseases with impaired ciliary clearance” (five items), “congenital malformations of the lung and tracheobronchial tree” (eight items), “lung transplantation and severe pulmonary diseases” (seven items), “recurrent asthma/wheezing attacks” (six items), and “intravenous administration” (four items). The final version of the questionnaire was accompanied by a short literature review on each topic.

Level of agreement for each statement was ranked on a 0–9 scale with 0 being total disagreement and 9 total agreement. Scores between 1 and 3 were considered to represent disagreement with the question contained in the statement, scores between 4 and 6 were regarded as neither agreement nor disagreement, and scores between 7 and 9 were regarded as agreement with the question proposed.

Selection of the Expert Panel

Experts were selected using convenience sampling method regarding their recognized experience in the field, based on being accredited members of the Spanish Society of Pediatric Pulmonology. Of 81 invited experts, 48 (59.3%) agreed to participate.

The fieldwork was carried out over a 12-week period from February 6 to April 23, 2012. The information was both manually delivered and sent electronically via e-mail

to each expert who accepted to participate in the study and a website with controlled access was available to fill out the questionnaire for each round. Responses collected through this link were anonymous.

Analysis and Interpretation of Data

For each item, the position of the median score of the group and the level of agreement reached by respondents were considered. Consensus was defined in the presence of concordance in the opinion of the panel, that is, when experts scoring out of the region of the three-point ranges ([1–3], [4–6], [7–9]) containing the median value were less than one-third of the respondents. In this case, the median value was taken to classify the group consensus reached: a majority of experts disagreed if the median value was ≤ 3 or a majority of experts agreed if the median value was ≥ 7 . When the median value was found in the 4–6 range, items were considered “doubtful” for a representative majority of the group. In contrast, no consensus due to “discordance” was considered when scores of a third or more of the panelist were found in the [1–3] range and scores of another third or more in the [7–9] range. An “indeterminate” level of consensus was established when neither concordance nor discordance was observed. The second round questionnaire included items “doubtful,” and item in which consensus was not reached because of “discordance” or “indeterminate” level of consensus in the first round as well as those items with a high dispersion of opinions among panelists (IQR ≥ 4).

Feedback was provided concerning the results of the first round. Respondents were provided with the median

group scores and were asked to re-evaluate items for which a consensus was not reached in the first round. The same analysis criteria were applied for the second round, *id est* consensus was finally defined when experts scoring in the region of the three-point ranges ([1–3], [4–6], [7–9]) containing the median value were “as much as” or “more than” two-third of the respondents, with an IQR equal or less than 4. In this case, the median value was taken to classify the group consensus reached: a majority of experts disagreed if the median value was ≤ 3 or a majority of experts agreed if the median value was ≥ 7 . When the median value was found in the 4–6 range, items were considered “doubtful” for a representative majority of the group. In contrast, “discordance” between the experts was considered when scores of a third or more of the panelist were found in the [1–3] range and scores of another third or more in the [7–9] range. Finally, an “indeterminate” level of consensus was established when neither concordance nor discordance was observed.

RESULTS

Of the 48 experts who participated in the study, 45 (93.7%) completed the two Delphi rounds. At the end of Round 1, consensus was obtained for 16/43 statements (37.2%) and at the end of Round 2, for a further eight statements. Overall, consensus was obtained for 24/43 statements (55.81%). Results obtained for each individual question are shown in Tables 1, 2, and 3.

The clinical scenario of “congenital malformations of the lung and tracheobronchial tree” showed the highest percentage of agreement. Consensus in agreement was reached in six of the eight statements (75%) (items #19, #21, #23, #24, #25, #26). Also, in the clinical scenario of “lung transplantation and severe pulmonary diseases,” consensus was obtained in four of the seven statements (57.1%), corresponding to the use of palivizumab in infants under 2 years of age, with indeterminate level of agreement for the prophylactic use of palivizumab in children between 2 and 4 years of age at the onset of the RSV epidemic season (items # 28, #30, #33). Similarly, in the clinical scenario of “cystic fibrosis and (CF) other diseases with impaired ciliary clearance,” the use of palivizumab in children older than 2 years of age would not be considered from the majority of the experts, with consensus against the statement for item #15 and disagreement for item #16. In contrast, a high level of agreement was obtained for the use of palivizumab for preventing RSV infection in infants diagnosed of cystic fibrosis until 24 months of age (item #14) and in infants with impaired ciliary clearance until 12 months of age (item #17).

In patients with neuromuscular diseases, a consensus was reached for the use palivizumab in patients with neuromuscular disease until 12 months and, when a

marked hypotonia was present, until 24 months of age (item #6), whereas no agreement was achieved for infants with severe central neurological conditions (#1, #2).

There was a high level of concordance in disagreement with the statements for items included in the clinical scenario of “asthma and/or recurrent wheezing,” with indeterminate level of consensus for only one question (item #39; healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, and having a negative asthma predictive index [API]²¹).

With regard to the use of palivizumab by the intravenous route, consensus in agreement with the statement was reached for the situation of established indication of prophylaxis when the intramuscular route is contraindicated (item #42), while 66.6% of experts found doubtful the intravenous administration of palivizumab as treatment of severe RSV infection in patients with severe underlying disease in which prophylaxis is not indicated (#43). More than 50% of experts manifested neither agreement nor disagreement for the intravenous use of palivizumab as treatment in infants with confirmed RSV infection and severe clinical condition in whom prophylaxis was not correctly administered either until 12 or 24 months of age. In the clinical scenario of “underlying systemic disease,” 82.9% of experts agreed for the use of palivizumab in patients with congenital or acquired immunodeficiency and respiratory involvement until 24 months of age and 79.4% agreed for treatment with palivizumab in infants with inborn errors of metabolism which lead to accumulation of material not metabolized and respiratory involvement until 12 months of age. For items about patients with polymalformative syndrome or chromosomal abnormalities consensus remained indeterminate (#7, #9, #10, and #13), with discordance within the experts for item #8: patients with polymalformative syndrome, without heart disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season.

DISCUSSION

The results of this Delphi process involving 48 experts throughout Spain showed a uniform level of concordance on more than half of statements, reflecting the off-label indications of palivizumab in clinical practice in infants with severe respiratory diseases. In the absence of robust scientific evidence, the extent to which clinicians agree on a given issue can be synthesized using consensus methodology. It was essential that as many of the specialists in Pediatric Pulmonology in Spain as possible were involved in the study, so that the recommendations resulting from this process, if any, had credibility and were a fair reflection of current opinion. The Delphi

TABLE 2—Consensus Achieved by Experts After Two Delphi Rounds: Panelists Out of the Three-Point Region That Includes the Median Score

According to the available evidence, your clinical experience, and personal knowledge, do you think that palivizumab may be indicated for the prophylaxis of respiratory syncytial virus (RSV) infection in the following clinical scenarios?	Median (IQR)	Panelists against the statement (%) ¹	[1–3] and [7–9] %	No consensus ²
Neuromuscular diseases				
1. Patients with severe central neurological conditions (hydrocephalus, central apneas, cerebral palsy, etc.) until 12 months of age at the onset of the RSV epidemic season	7 (3)	42.9		Indeterminate
2. Patients with severe central neurological conditions (hydrocephalus, central apneas, cerebral palsy, etc.) until 24 months of age at the onset of the RSV epidemic season	5 (4)	85.3	44.1–41.2	Disagreement
4. Patients with neuromuscular disease with marked hypotonia until 24 months of age at the onset of the RSV epidemic season	7 (4)	45.5		Indeterminate
Underlying systemic disease				
7. Patients with polymalformative syndrome, without heart disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season	7 (3)	48.6		Indeterminate
8. Patients with polymalformative syndrome, without heart disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season	6 (4)	77.8	38.9–38.9	Disagreement
9. Patients with chromosomal anomaly, without heart disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season	7 (3)	45.7		Indeterminate
10. Patients with chromosomal anomaly, without heart disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season	5 (2)	51.5		Indeterminate
13. Patients with dense deposit disease, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season	6 (4)	71.4		Indeterminate
Cystic fibrosis and other diseases with impaired ciliary clearance				
16. In patients with severe disease and carriers of chronic infection with <i>Pseudomonas aeruginosa</i> prophylaxis should be extended up to 4 years of age at the onset of the RSV epidemic season	5 (4)	82.9	40.0–42.9	Disagreement
18. Patients with diseases involving impaired ciliary clearance (ciliary dyskinesia, bronchiectasis unrelated to cystic fibrosis, etc.) until 24 months of age at the onset of the RSV epidemic season	7 (6)	36.1		Indeterminate
Congenital anomalies of the lung and tracheobronchial tree				
20. Patients operated on for esophageal atresia and/or tracheoesophageal fistula until 24 months of age at the onset of the RSV epidemic season	7 (5)	48.6		Indeterminate
22. Patients with severe tracheomalacia until 24 months of age at the onset of the RSV epidemic season	7 (4)	34.3		Indeterminate
Lung transplantation and severe pulmonary diseases				
28. Lung transplant recipients until 4 years of age at the onset of the RSV epidemic season	6 (2)	55.6		Indeterminate
30. Patients in the waiting list for lung transplantation under 4 years of age at the onset of the RSV epidemic season	7 (2)	41.7		Indeterminate
33. Patients with idiopathic pulmonary hypertension under 4 years of age at the onset of the RSV epidemic season	3 (2)	41.7		Indeterminate
Asthma/recurrent wheezing				
39. Healthy infant under 1 year of age at the onset of the RSV epidemic season, born at term, who had presented two or more episodes of wheezing prior to RSV infection season, and negative API	3 (2)	37.1		Indeterminate

(Continued)

Table 2—(Continued)

According to the available evidence, your clinical experience, and personal knowledge, do you think that palivizumab may be indicated for the prophylaxis of respiratory syncytial virus (RSV) infection in the following clinical scenarios?	Median (IQR)	Panelists against the statement (%) ¹	[1–3] and [7–9] %	No consensus ²
Intravenous administration				
40. Patients with indication of prophylaxis in which prophylaxis was not correctly administered, with confirmed RSV infection and severe clinical condition as treatment of RSV, until 12 months of age at the onset of the RSV epidemic season	5 (2)	38.2		Indeterminate
41. Patients with indication of prophylaxis in which prophylaxis was not correctly administered, with confirmed RSV infection and severe clinical condition as treatment of RSV, until 24 months of age at the onset of the RSV epidemic season	5 (1)	35.2		Indeterminate
43. Patients with severe underlying disease in which prophylaxis is not indicated, as treatment of severe RSV infection	5 (2)	33.4		Doubtful

IQR, interquartile range.

¹Panelists against the statement (%).

²See materials and methods for details.

technique has very few geographical limitations as it primarily uses postal questionnaires, which enabled a large number of pediatric respiratory diseases specialists to take part at a relatively little cost. This methodology also allows a degree of anonymity, which helps to avoid domination by an individual or coalitions with vested interests or strong opinions. The process of rounds also allows individuals to be aware of the distribution of the group's responses and to modify their own previous response in light of this. There is no standard threshold for consensus, however, previous Delphi studies have accepted consensus levels between 50% and 80%.²² Our study addressed an important area of pediatric practice of respiratory medicine and it was felt appropriate to set a threshold for concordance when the answer of 66% of the participant felt in the same three-point region (1–3), (4–6), (7–9), and a level of agreement for a median at the 7–9 range using a 9-point Likert-type scale, a scale using fixed choice response formats designed to measure attitudes or opinions.^{10–19}

Different authors and European, North American, and Australian clinical guidelines recommend passive immunization with palivizumab in children with clinically relevant neuromuscular impairment because of their increased risk for severe RSV disease.^{23–26} In our study, consensus in agreement was reached for the use of palivizumab in infants with neuromuscular disease until 12 months of age at the onset of the RSV epidemic season and until 24 months of age in the presence of neuromuscular impairment associated with marked hypotonia. However, consensus was not reached for respiratory conditions secondary to central nervous

system disorders (severe hydrocephalus, cerebral palsy, etc.). Congenital malformations of the respiratory system as well as heart disease or malformation of central nervous system and compromised immune function are well-known risk factors associated with RSV during the RSV season.^{4,27–32} In the present study, panelists agreed with the indication of palivizumab in infants with congenital or acquired immunodeficiency disorders and respiratory involvement until 24 months of age and in those with inborn errors of metabolism and respiratory compromise until 12 months of age.

Respiratory infection including RSV disease has been shown to play an important role in the steady decline of respiratory function in cystic fibrosis.^{33,34} Moreover, there is a synergism between RSV infections and *Pseudomonas aeruginosa* in cystic fibrosis lung disease.³⁵ According to Winterstein et al.³⁶, RSV hospitalization incidence for RSV infection in CF patients seems to be low and, though unadjusted and adjusted RSV-hospitalization incidence rates suggested potentially positive effects of palivizumab, results are inconclusive due to small event rates. On the other hand, according to Robinson et al.³⁷, it is not possible to draw conclusions on the safety and tolerability of RSV prophylaxis with palivizumab in infants with cystic fibrosis because no good trials have been done to access this point, but it seems that in CF patients the overall incidence of adverse events is similar to other groups. On a similar way, there is currently no evidence from randomized studies that influenza vaccine given to patients with cystic fibrosis is of benefit to them.³⁸ Nevertheless, immunization against seasonal influenza virus is recommended in several

TABLE 3—Summary of Consensus About Off-Label Uses of Palivizumab in the Prevention of RSV Infection in Children With Some Severe Respiratory Diseases as Achieved by Experts After Two Delphi Rounds

1. Patients with neuromuscular disease until 12 months of age at the onset of RSV epidemic season. When a marked hypotonia is present, until 24 months of age
2. Patients with congenital or acquired immunodeficiency, with respiratory involvement until 24 months of age at the onset of the RSV epidemic season
3. Patients with storage disease, with respiratory involvement until 12 months of age at the onset of the RSV epidemic season
4. Patients diagnosed of cystic fibrosis until 24 months of age at the onset of the RSV epidemic season
5. Patients with diseases involving impaired ciliary clearance (ciliary dyskinesia, bronchiectasis unrelated to cystic fibrosis, etc.) until 12 months of age at the onset of the RSV epidemic season
6. Patients operated on for esophageal atresia and/or tracheoesophageal fistula until 12 months of age at the onset of the RSV epidemic season
7. Patients with severe tracheomalacia until 12 months of age at the onset of the RSV epidemic season
8. Patients with chronic respiratory insufficiency who were operated on for severe congenital diaphragmatic hernia in the neonatal period until 24 months of age at the onset of the RSV epidemic season
9. Patients with bronchopulmonary malformations and respiratory symptoms until 24 months of age at the onset of the RSV epidemic season
10. Lung transplant recipients until 24 months of age at the onset of the RSV epidemic season
11. Patients in the waiting list for lung transplantation under 2 years of age at the onset of the RSV epidemic season
12. Patients with oxygen-dependent severe interstitial pulmonary disease or bronchiolitis obliterans under 2 years of age at the onset of the RSV epidemic season
13. Patients with idiopathic pulmonary hypertension under 2 years of age at the onset of the RSV epidemic season
14. Patients with established indication of prophylaxis in which the use of the intramuscular route is contraindicated may have i.v. administration

clinical guides for cystic fibrosis.³⁹ Therefore, in the absence of effective antiviral therapy, children with cystic fibrosis are candidates for prophylaxis against preventable viral diseases, either passive immunoprophylaxis as for RSV infection, or vaccination as for influenza infection.^{10,40,41} We found that 86% of experts justified prophylaxis with palivizumab at the onset of the RSV season in infants with cystic fibrosis under 2 years of age, but not to maintain prophylaxis up to 4 years of age. In patients with cystic fibrosis and chronic *P. aeruginosa* infection aged between 2 and 4 years, consensus was not reached. On the other hand, the expert group agreed in the use of palivizumab in patients with impaired ciliary function under 12 months of age, although in infants until 24 months of age, consensus remained borderline and the item was classified as indeterminate.

Infants with congenital lung and tracheobronchial tree malformation have shown a higher morbidity and mortality rates associated with RSV infection as compared with healthy infants.^{29,42} Although controlled studies on the efficacy of palivizumab in infants with congenital respiratory malformation are lacking, clinical guidelines recommend the use of palivizumab in this population.²⁴ In the Canadian prospective, observational, registry of 5,286 infants at high risk for RSV who received at least 1 dose of palivizumab during the 2005–2009 RSV seasons, besides prophylaxis for prematurity, bronchopulmonary dysplasia/chronic lung disease, or congenital heart disease, 11.1% of infants were prophylaxed for “other reasons,” 19.7% of which were congenital abnormalities of the respiratory tract.⁴³ Moreover, between 2005 and 2009, these “other indications” increased progressively from 4.4% to 14.9% of the cases. In our study, immunoprophylaxis with palivizumab was consensuated for the clinical scenario of infants operated on for esophageal atresia and/or tracheoesophageal fistula under 12 months of age, whereas in the same scenario of infants until 24 months of age, immunoprophylaxis was recommended by only 51.4% of experts and consensus was not reached. The same findings were obtained for the indication of palivizumab in infants with severe tracheomalacia. However, in infants undergoing surgery for congenital diaphragmatic hernia, as well as in patients with bronchopulmonary malformations and respiratory symptoms, consensus in the use of palivizumab was extended to infants until 24 months of age at the onset of the RSV epidemic season.

Lung transplant recipients with viral respiratory infection (paramyxovirus, influenza, adenovirus, human metapneumovirus) are at risk of complications, including bronchitis, pneumonia, acute graft rejection, and bronchiolitis obliterans,^{44–46} but controlled studies regarding the usefulness of passive immunization with palivizumab have not been published in the literature.²⁴ In a survey of 108 pediatric solid-organ transplant centers, 49% of programs reported using RSV prophylaxis, with palivizumab used at 97% of centers. Prophylaxis was provided to infants aged 0–12 months by 93% of responding centers and 79.3% of centers extended its use to infants aged 0–24 months.⁴⁷ In the subgroup of lung transplantation, palivizumab was administered to 25% of candidates and 50% of recipients.⁴⁷ In a survey of members of the International Pediatric Lung Transplant Collaborative regarding RSV prevention and treatment strategies, many centers offered prophylaxis and treatments, but strategies are not uniform.⁴⁸ In the present study, consensus was reached for the indication of palivizumab in lung transplant recipients until 24 months of age at the onset of the RSV season and in candidates for lung transplantation less than 2 years of age. However, consensus was not reached for the same clinical practice in children until they are 4 years old. On the other hand,

because of the rarity of interstitial lung diseases in childhood, the indication of palivizumab in this setting is unknown. In fact, given the confirmed benefit of palivizumab in other chronic respiratory diseases, such as bronchopulmonary dysplasia, it may be extrapolated that infants under 2 years of age with severe oxygen-dependent interstitial lung disease, such as those associated with surfactant protein deficiency, may also benefit from the prophylactic use of palivizumab. In addition, although data on immunoprophylaxis in infants with idiopathic pulmonary hypertension are lacking, it may be speculated that prophylaxis with palivizumab may be useful given the benefit of palivizumab in infants and young children with pulmonary hypertension secondary to congenital heart disease.^{11,49,50} In this study, there was agreement among the experts to the use of palivizumab in patients with severe oxygen-dependent interstitial lung disease or bronchiolitis obliterans and in infants with idiopathic pulmonary hypertension younger than 2 years of age at the beginning of the RSV season. Agreement regarding maintenance of immunoprophylaxis in children with idiopathic pulmonary hypertension less than 4 years of age was not obtained.

Children who experience RSV lower respiratory tract infections early in life have high rates of subsequent recurrent wheezing. By preventing RSV lower respiratory tract infection, two studies of respiratory outcomes in an international cohort have provided evidence of the usefulness of palivizumab in protecting against recurrent wheezing in premature infants without chronic lung disease.^{51,52} In one of these studies, however, there was no effect of palivizumab in children with a family history of atopy or food allergies.⁵² In our study, experts were asked for the indication of prophylaxis with palivizumab in healthy infants born at term at risk of recurrent wheezing evaluated by the API or with history of two or more episodes of wheezing prior to the RSV season, with or without family history of atopy, and positive API. In all these clinical scenarios, experts coincided in considering inadequate the indication of prophylaxis with palivizumab. However, in the case of healthy infants born at term with history of two or more episodes of wheezing and negative API, consensus was not reached.

The use of palivizumab by intravenous infusion is not included in the product's technical specifications but this route of administration has been used in both pediatric and adult patients for the treatment of RSV infection in the presence of comorbidities (congenital heart disease, oncohematological disorders, recipients of hematopoietic stem cell transplants, prematurity, etc.)⁵³⁻⁵⁶ as well as for preventing RSV infection in immunosuppressed patients older than 2 years of age in which the intramuscular route was contraindicated.⁵⁷ The use of palivizumab as treatment of RSV infection is controversial and frequently has been used in combination with ribavirin.^{58,59} In the present study, consensus was only reached for intravenous

administration of palivizumab in patients with established indication of prophylactic use in whom the intramuscular route was contraindicated.

As limitations of the study it should be pointed out the lack of concordance in up to 44.19% of the statements. This could reflect the uncertainty of the experts due to the small amount of data available in the literature or to the lack of personal experience about the use of palivizumab in the clinical setting analyzed. On the other hand, the items on which concordance was achieved could be the clinical setting in which either more studies have been done or more reasonable seems to be the use of palivizumab. Being aware that only a grade C recommendation can be made based on expert opinion and panel consensus, the authors consider that in the absence of studies with highest grade of evidence, consensus driven clinical guidelines represent a starting point to design new prospective studies aimed to achieve better knowledge on the real effect of preventing RSV infection with palivizumab, in small children with severe respiratory disorders. This consensus may not change substantially the clinical practice, but clinicians who are in doubt about the indication of immunoprophylaxis because of the off-labeled use of palivizumab in pediatric patients with severe respiratory disease, may feel more confident. Moreover, a prospective evaluation of the effectiveness of the use of palivizumab in young patients with severe respiratory disease should be encouraged. As the use of palivizumab is very similar in many European countries and North America, we believe that the results of this study should be of interest outside Spain and its application in other countries feasible.

CONCLUSION

The Delphi process was used in finding consensus for off-label uses of palivizumab in the prevention of RSV infection in children with some severe respiratory diseases (Table 3). The lack of controlled clinical trials and the difficulty of performing clinical trials in the near future, make necessary to have available data provided by expert consensus studies supporting the more rational use of resources. The applicability of the present results to clinical practice should be evaluated individually and reviewed periodically in the light of new emerging evidence. Moreover, further studies are needed to add evidence to the most frequent and clinically oriented scenarios that have shown higher levels of uncertainty.

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Scientific Committee: Mirella Gaboli, Òscar Asensio de la Cruz, María Isabel Barrio Gómez de Agüero, Antonio Moreno Galdó, Guadalupe Pérez Pérez, and Manuel Sánchez-Solís de Querol.

Expert Group: Domingo Álvarez Gil, Anselmo Andrés Martín, Carmen Antelo Landeira, Òscar Asensio de la Cruz, María Isabel Barrio Gómez de Agüero, José Batlles Garrido, Rosa María Busquets Monge, Gonzalo Cabrera Roca, Alicia Callejón Callejón, Manuel Carrasco Zalvide, Isidoro Cortell Aznar, J. Javier Elorz Lambarri, Amparo Escribano Montaner, Juan Figuerola Mulet, Mirella Gaboli, M^a Luz García García, M^a Gloria García Hernández, Silvia Gartner Tizzano, David Gómez-Pastrana Durán, Eduardo González Pérez-Yarza, Juan Pedro González Valencia, Javier Korta Murua, M^a del Mar Lertxundi Etxebarria, Juan Alonso López Andreu, M^a Carmen Luna Paredes, F. Javier Mintegui Aramburu, Antonio Moreno Galdó, Martín Navarro Merino, Concepción Olivia Hernández, Borja Osona Rodríguez de Torres, María Teresa Pascual Sánchez, María Dolores Pastor Vivero, Francisco Javier Pérez Frías, Guadalupe Pérez Pérez, Estela Pérez Ruiz, María Teresa Rubí Ruiz, Santiago Rueda Esteban, Antonio Salcedo Posadas, Adolfo Sánchez Marengo, Ernesto Sánchez Sánchez, Manuel Sánchez-Solís de Querol, Adolfo Sequeiros González, Josep Sirvent Gómez, José Valverde Molina, Carlos Vázquez Cordero, María del Valle Velasco González, José Ramón Villa Asensi, and Gerardo Vizmanos Lamotte.

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