

## AEROBIC BACTERIA, *CHLAMYDIA TRACHOMATIS*, *PNEUMOCYSTIS CARINII* AND *CYTOMEGALOVIRUS* AS AGENTS OF SEVERE PNEUMONIA IN SMALL INFANTS

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### SUMMARY

The authors studied 58 infants hospitalized for pneumonia in a semi-intensive care unit. Age ranged from 1 complete to 6 incomplete months. The infants were sent from another hospital in 20 cases and from home in a further 38. Pulmonary involvement, which was alveolar in 46 cases and interstitial in 12, was bilateral in 31 children. The investigation was carried out prospectively on the etiological agents associated with respiratory infection to look for evidence of aerobic bacteria (blood cultures), *Chlamydia trachomatis* and *Cytomegalovirus* (serology), and *Pneumocystis carinii* (direct microscopy of tracheal aspirated material). The following infectious agents were diagnosed in 21 children (36.2%): Aerobic bacteria (8), *Chlamydia trachomatis* (5), *Pneumocystis carinii* (3), *Cytomegalovirus* (3), *Cytomegalovirus* and *Chlamydia trachomatis* (1), Aerobic bacteria and *Cytomegalovirus* (1). Seven cases of infection by *Chlamydia trachomatis* and/or *Cytomegalovirus* were diagnosed out of the 12 cases with pulmonary interstitial involvement.

**KEYWORDS:** Pneumonia; Etiology; Infant.

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### INTRODUCTION

Pulmonary infections account for 10% of the deaths among Brazilian infants under 1 year of age<sup>41</sup>. For several developing countries, mortality by pneumonia is even more significant<sup>40</sup>. Multinational health organizations have directed specific programs to counteract the morbidity and mortality caused by infection in the lung and lower airways<sup>11, 35, 55, 62</sup>. The strategy adopted in developing countries involves prevention, detection, and treatment of cases<sup>3, 10, 16</sup>. Several studies have been carried out to identify the most common etiological agents to establish appropriate therapeutics<sup>30, 43, 50</sup>. Pneumonia in these countries is predominantly bacterial, caused by

*Streptococcus pneumoniae* and *Haemophilus influenzae*, although other bacteria (*Staphylococcus aureus* and gram negative enteric bacilli) may also be found<sup>6, 23, 24</sup>.

Knowledge about the etiology of pneumonias in the first months of life in developing countries is limited<sup>6, 25, 56</sup>. The etiological spectrum of infection of the lower airways in young infants has expanded in the last two decades<sup>4, 9, 47, 54</sup>. Some agents have been recognized as significant for this age bracket: *Chlamydia trachomatis*, *Cytomegalovirus*, and *Pneumocystis carinii*<sup>54, 60</sup>. Genital mycoplasmas, *Ureaplasma urealyticum*, and *Mycoplasma*

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Informed consent was obtained from the parents or guardians. The present investigation was carried out in accordance with the ethical norms approved for research by The Children's Institute of the Pediatrics Department of the School of Medicine of the University of São Paulo.

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*hominis* may also play a role in the genesis of pulmonary infections occurring in this period<sup>54, 59</sup>. In developed countries, pulmonary infections caused by these pathogens are generally afebrile, subacute in course, with reduced systemic repercussion and satisfactory evolution, although severe cases have been described<sup>54, 60</sup>. Conversely, in developing countries, data concerning infection caused by those agents of afebrile pneumonia are rare<sup>6, 56, 59</sup>.

The authors carried out a prospective study to evaluate the occurrence of potential pulmonary pathogens in a group of socio-economically deprived infants, hospitalized in a semi-intensive care unit for severe pneumonia. *Chlamydia trachomatis*, *Cytomegalovirus*, *Pneumocystis carinii*, and aerobic bacteria were investigated.

### SAMPLING AND METHODS

A prospective study was carried out over a two-year period (January 1986 to December 1987), including infants aged from 1 complete to 6 incomplete months, who had been hospitalized with pneumonia in the semi-intensive care unit of the Children's Institute of the Pediatrics Department of the School of Medicine of the University of São Paulo. Selection criteria for inclusion in the sample were: a) A history of acute respiratory disease (coughing and/or shortness of breath for less than seven days) as main complaint for hospitalization. b) Respiratory rate higher than 60 times per minute. c) Radiographic exam revealing alveolar or interstitial pulmonary alteration (all of the evaluations were carried out by the same pediatric radiologist).

Infants matching the three following conditions were excluded: a) Manifestations of systemic infection: scleredema, hemorrhagic syndrome, and alteration in the level of consciousness. b) Concomitant diarrheic disease or urinary infection. c) Malformation of the central nervous system, of the cardiorespiratory system, and other chronic pathologies such as mucoviscidosis and AIDS. A total of fifty-eight children were selected.

Materials were obtained upon hospitalization. The pathogens investigated and the methods used were: a) *Pneumocystis carinii*: tracheal secretions were collected by gentle aspiration with a sterile polyethylene cannula attached to a disposable syringe guided by direct laryngoscopy and fixed at the bedside. The material fixed on slides was examined by direct microscopy with use of the coloring by toluidine blue technique<sup>21</sup>. b) *Chlamydia*

*trachomatis*: Serological examination was carried out to estimate the amount of specific antibodies of the IgM class. The method used was indirect immunofluorescence<sup>45</sup>, and a dilution titer greater or equal to 1/32 was regarded as positive. c) *Cytomegalovirus*: Serological examination was performed to assess the IgM-specific antibody titer. The method employed was an immunoenzymatic assay<sup>26</sup>. Tests with a difference of absorbance greater or equal to 0.2 were regarded as positive. d) Aerobic bacteria: Blood culture (three independent samples) in tryptic soybean medium was conducted<sup>31, 34</sup>. Additional examinations were performed: hemogram, HIV serology, urine culture and analysis of sediment as well as assessment of arterial gases, seric electrolytes, and rheumatoid factor. A statistical analysis of the frequencies obtained was conducted by means of a calculation of the binomial distribution ( $p = .05$ ). The Fischer exact test was utilized for qualitative variables.

### RESULTS

The fifty-eight children, 33 male and 25 female, who met the criteria for selection and were included in the study are described in Table 1.

TABLE 1  
Clinical and laboratory characteristics in 58 infants hospitalized with pneumonia (\*)

1. Age (months)	X = 2.3 (SD=1.3)
2. Weight at birth (grams)	X = 2,706 (SD=716)
3. Type of delivery	normal: 40, caesarean: 18
4. Time of history (days)	X = 5.9 (SD=4.4)
5. Interned in another hospital in the 20 days prior	20
6. Previous use of antimicrobial (7 days prior)	23
7. Weight (grams)	X = 3,320 (SD=817)
8. Rate of breathing $\geq$ 60 times/minute	58
9. Partial O <sub>2</sub> pressure on hospitalization (mmHg)	X = 63.2 (SD=16.1)
10. Partial CO <sub>2</sub> pressure on hospitalization (mmHg)	X = 37.1 (SD=11.5)
11. Leucogram $>$ 10,000 cells/mm <sup>3</sup> on hospitalization	36
12. Leucogram between 5,000 and 10,000 cells/mm <sup>3</sup> on hospitalization	22
13. Blood eosinophiles $>$ 300 cells/mm <sup>3</sup> on hospitalization	10
14. Fever during first 10 days of hospitalization (days)	X = 2.7 (SD=3.6)
15. Period of hospitalization (days)	X = 22.8 (SD=30.8)
16. Deaths	3

(\*) Notations: X = Average, SD = Standard Deviation

The radiographic aspect obtained on hospitalization was of lobar condensation (1 case), bronchopneumonia (45 cases), and interstitial involvement (12 cases). In 31 children, the pulmonary commitment was bilateral, and in 27, unilateral. Twenty-three pathogens were diagnosed in 21 children (36.2%). The bacteria found in blood cultures were: *Staphylococcus aureus* (2 cases), *Haemophilus influenzae* (1), *Streptococcus pneumoniae* (1), *Streptococcus pyogenes* (1), *Klebsiella pneumoniae* (1), *Pseudomonas aeruginosa* (1), *Acinetobacter calcoaceticus* (1), gram negative bacillus not identified (1). Infection by *Chlamydia trachomatis* was diagnosed in 6 children and by *Cytomegalovirus* in 5 cases. *Pneumocystis carinii* was found in tracheal material in 3 infants. The results are included in Table 2.

After hospital discharge fifty-five cases were followed up as outpatients until the complete clinical and radiological resolution. Three infants died during hospitalization.

## DISCUSSION

A potential pathogen was detected in 21 cases (36.2%) out of a group of 58 children with severe pneumonia. Two agents were detected in two of the children. The percentage of cases with an etiological identification and the association of infectious agents proved similar to those observed other authors who evaluated the etiology of infection of the lower airways in infants in developing countries<sup>6, 48</sup>. The pathogenic agents were, at times, identified in a greater proportion of cases<sup>19, 49</sup>. The present study diverges in part from others in what refers to the etiological agents generally researched in infants in developing countries<sup>6, 28, 48</sup>; not only were extra-

cellular bacteria investigated but also pathogens not ordinarily studied: *Chlamydia trachomatis*, *Cytomegalovirus* and *Pneumocystis carinii*<sup>56, 58</sup>. These three agents were diagnosed together in 13 out of the 58 children studied (22.4%). The estimate of frequency of this proportion is between 12.5 and 35.3% (at a confidence level of .95). These pathogens, known as agents of infant afebrile pneumonia, were associated to a significant percentage of the cases studied. Several etiological studies that evaluated infections caused by respiratory viruses, extracellular bacteria, and *Mycoplasma pneumoniae* in infants with pneumonia presented a significant proportion of cases without etiological explanation<sup>3, 14, 15</sup>. These agents of acute afebrile pneumonia might have been responsible for some of the cases with no recognized etiology<sup>20, 62</sup>. In our study, these pathogens were associated to 7 out of the 12 infants with interstitial pulmonary involvement (58.3%) and in 5 out of 45 children (11.1 %) with alveolar commitment. One case of mixed infection (*Cytomegalovirus* and *Acinetobacter calcoaceticus*) was excluded from this analysis. This distribution was found to be statistically significant at a level of  $p = .05$ . The result observed is in accordance with previous references that associate agents of afebrile pneumonia in infants to interstitial pulmonary involvement<sup>42, 54</sup>. The combined occurrence of these three pathogens is also recognized<sup>54</sup>. It is interesting to observe that agents of afebrile pneumonia were detected in young infants with severe alveolar involvement<sup>53, 54</sup>. As to finding the aerobic bacteria in 9 children (15.5%), results are similar to those of other publications, although severe pneumonias may be associated to a greater number of cases with bacteremia<sup>19, 52</sup>. For developing countries a preponderance of extracellular

TABLE 2  
Number and estimate of frequency (\*) of the pathogens in 58 infants with pneumonia hospitalized in a semi-intensive care unit.

Pathogens	Number		Estimate of Frequency (%)
	Raw	%	
Extracellular bacteria	8	13.8	6.1 to 25.4
<i>Chlamydia trachomatis</i>	5	8.6	2.9 to 19.0
<i>Pneumocystis carinii</i>	3	5.2	1.1 to 14.4
<i>Cytomegalovirus</i>	3	5.2	1.1 to 14.4
<i>Cytomegalovirus</i> and <i>Chlamydia trachomatis</i>	1	1.7	0.1 to 9.2
Extracellular bacteria and <i>Cytomegalovirus</i>	1	1.7	0.1 to 9.2
Not determined	37	63.8	50.0 to 76.0
Total	58	100	

(\*)  $p = .05$

bacteria as the most important etiological agents for the infants with severe pneumonia is widely accepted<sup>18, 49, 50, 51</sup>.

The number of cases with etiological explanation for the group investigated would be higher if we had estimated other pathogenic agents, or if the investigation had included other biological materials<sup>8, 39, 61</sup>. In former studies carried out in our hospital, we detected extra cellular bacterial agents in the majority of cases<sup>13, 44</sup>. Bacterioscopic examination and culture of the material obtained by aspirative pulmonary puncture were carried out in these investigations; however, aspirative pulmonary puncture is today a reason for controversy<sup>2, 27, 37</sup>. Bronchoalveolar washings have also resulted in an increase in the number of cases with an etiological explanation even though experience with this procedure in infants is limited<sup>12, 29</sup>.

Respiratory viruses such as *Syncytial Respiratory Virus*, *Parainfluenza*, *Influenza* and *Adenovirus* have been associated to the etiology of pneumonias in developing countries, with a frequency between 10 and 50% of the cases<sup>6, 19, 33, 57</sup>. In a previous study with infants hospitalized with pneumonia, we carried out culture of material obtained from the oropharynx and from the lung (by aspirated pulmonary puncture) as well as serological examinations, detecting 21.2% of cases with viral agent<sup>14</sup>.

The association virus-bacteria and virus-agent of afebrile pneumonia is frequent<sup>15, 32, 51, 54</sup>. Thus, an evaluation of viral agents in the present investigation would certainly increase the etiological identification and might perhaps identify mixed infections<sup>1, 5, 48, 49</sup>. Research on *Mycoplasma pneumoniae* through culture of material obtained from the airways or serological examination shows positive results in a small percentage of infants with infection of the lower airways<sup>38</sup>. In a previous study, we did not detect the agent in material obtained from the oropharynx, pulmonary aspirate, or through a serological examination, but the number of cases was small<sup>14</sup>. Other mycoplasmas are being assessed for their pathogenic role for the lower airways<sup>59</sup>.

The authors observed that in the young deprived infants, hospitalized with severe pneumonia, aerobic bacteria predominated as etiological agents and that a percentage of cases were associated to the agents of afebrile pneumonia<sup>20</sup>. The investigation of the role of other infectious agents for this age bracket should continue<sup>7, 17, 22, 36, 46</sup>.

## RESUMO

### **Bactérias aeróbias, *Chlamydia trachomatis*, *Pneumocystis carinii* e *Cytomegalovirus*: agentes causadores de pneumonia grave em pequenos lactentes.**

Os autores estudaram prospectivamente 58 lactentes internados por pneumonia em unidade semi-intensiva. A idade foi limitada entre 1 mês completo e 6 meses incompletos. A procedência das crianças foi de outro hospital em 20 casos e domiciliar em 38. O acometimento pulmonar era alveolar em 46 casos, intersticial em 12 e bilateral em 31 crianças. Foram pesquisados agentes etiológicos associados à infecção respiratória dos lactentes jovens: Bactérias aeróbias (Hemoculturas), *Chlamydia trachomatis* e *Cytomegalovirus* (sorologia), e *Pneumocystis carinii* (microscopia direta do aspirado traqueal). Foram diagnosticadas infecções em 21 crianças (36,2%): Bactérias aeróbias (8), *Chlamydia trachomatis* (5), *Cytomegalovirus* (3), *Pneumocystis carinii* (3), *Cytomegalovirus* e *Chlamydia trachomatis* (1), Bactéria aeróbia e *Cytomegalovirus* (1). Foram diagnosticadas 7 infecções por *Chlamydia trachomatis* e/ou *Cytomegalovirus* entre as 12 crianças com quadro intersticial.

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