Exclusive Breastfeeding Protects Against Bacterial Colonization and Day Care Exposure to Otitis Media

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ABSTRACT. Objective. We followed a cohort (N = 306) of infants at well-baby visits in two suburban pediatric practices to assess the relation of exclusive breast-feeding, and other environmental exposures, to episodes of acute otitis media (AOM) and otitis media with effusion (OME).

Methods. Detailed prospective information about the exclusiveness of breastfeeding, parental smoking, day care attendance, and family history was obtained at scheduled clinic visits. Tympanometric and otoscopic examinations were used in the diagnosis of otitis media (OM). Nasopharyngeal cultures were performed at 1–6 months, and at 8, 10, 12, 15, 18, and 24 months of age to detect colonization with middle-ear pathogens.

Results. Between 6 and 12 months of age, cumulative incidence of first OM episodes increased from 25% to 51% in infants exclusively breastfed and from 54% to 76% in infants formula-fed from birth. Peak incidence of AOM and OME episodes was inversely related to rates of breastfeeding beyond 3 months of age. A twofold elevated risk of first episodes of AOM or OME was observed in exclusively formula-fed infants compared with infants exclusively breast-fed for 6 months. In the logistic regression analysis, formula-feeding was the most significant predictor of AOM and OME episodes, although age at colonization with middle-ear pathogens and day care (outside the home) were significant competing risk factors. A hazard health model suggested additionally that breastfeeding, even for short durations (3 months), reduced onset of OM episodes in infancy.

Conclusions. Modifiable factors in the onset of AOM and OME episodes during the first 2 years of life include early age at colonization (<3 months of age), day care outside the home, and not being breastfed. Pediatrics 1997;100(4). URL: http://www.pediatrics.org/cgi/content/full/100/4/e7; acute otitis media; otitis media with effusion; nasopharyngeal colonization; breastfeeding; day care; proportional hazards.

ABBREVIATIONS. AOM, acute otitis media; OME, otitis media with effusion; OM, otitis media; CI, confidence interval; RR, relative risk.

D espite general agreement that breastfeeding moderates gastrointestinal and respiratory infections in childhood, many questions underlying the beneficial effects of breast milk in preventing acute otitis media (AOM) and otitis media with effusion (OME) remain unanswered. Design issues and sample size variation account for much of the variability reported. Summarized in Table 1, recent studies in well-defined cohorts have yielded equivocal results. Among 5336 infants in Turku, Finland, followed for 1 year, those with breastfeeding durations of <9 months were associated with a 30% to 50% elevated risk of developing otitis media (OM). A cohort of 1661 infants born in Dunedin, New Zealand, were assessed at 3 years of age; after adjustment for number of siblings, type of day care, and passive smoking, duration of breastfeeding was associated with reduced prevalence of OM disease, but the difference was not significant. In Greater Boston, among 877 children still being followed at 1 year of age, breastfeeding was found to be significantly protective for one or more episodes (odds ratio = 0.64; 95% confidence interval [CI]: 0.44–0.91). In another large cohort of 2130 children still being followed at 2 years, breastfeeding for <3 months was associated with a 20% to 60% elevated risk of AOM and OME. A metaanalysis of recent follow-up studies concluded that breastfeeding even for 3 months was protective in decreasing the risk of OM.

In the United States, the bacteria most predominantly associated with OM infections in childhood include Streptococcus pneumoniae, nontypeable Haemophilus influenzae, and Moraxella catarrhalis. Bac terial infections are thought to play a more significant role in AOM compared with OME. Given the problem of recognizing the occurrence of OME and measuring the duration of an asymptomatic event, however, the role of bacterial and viral infection in OME needs additional study.

The present study was, in part, designed to examine the role of breastfeeding relative to selected risk factors, including host susceptibility (age, gender), colonization with potential pathogens, parental smoking, and day care exposures, in identifying a subgroup of infants at greatest risk of AOM and OME. Using otoscopy and tympanometry to diagnosis OM episodes, we followed intensively a cohort of infants from birth through 24 months of age. Beneficial effects of human milk were assessed at the end of the first and second years of life. Outcomes in-
in the major feeding groups (exclusive or partially breastfed, exclusive formula); (2) effect of breastfeeding on delaying age at colonization (>3 months) and first episodes of OM; and (3) changes to risk of AOM and OME after breastfeeding is discontinued.

METHODS AND PROCEDURES

Study Population

A cohort of 306 infants were enrolled consecutively at well-baby visits shortly after birth in two large pediatric practices in Buffalo, NY. Infants with craniofacial abnormalities, genetic disorders, and immune deficiencies were excluded from the study. Informed consent was obtained from all maternal guardians at entry, and infants were followed intensively monthly for the first 6 months of life, and then at 8, 10, 12, 15, 18, 21, and 24 months of age. Cumulative incidence of OM episodes and colonization patterns of disease in this present cohort are described in detail in recent reports.12–14 Interim visits after diagnosis of middle-ear disease were performed at children ≥6 months of age; the lowest negative pressure on the tympanometer used was −400 daPa.

AOM was defined by presence of one or more symptoms such as fever, irritability, ear pain, pulling at the ears, and tympanic membrane changes including increased thickness, bulging, loss of landmarks, decreased mobility, and a flattened tympanogram, type b curve.12 Tympanograms were performed in children ≥6 months of age; the lowest negative pressure on the tympanometer used was −400 daPa.

OME was defined as the presence of a middle-ear effusion in the absence of symptoms. The tympanic membrane was not thickened, but it was immobile and the tympanogram had to show a flattened tracing in children >6 months of age. In our study, de novo OME episodes appeared spontaneously and were not related to a preceding episode of AOM. For episodes of either AOM or OME, children were examined monthly until the ear examination was entirely normal; duration was calculated from the start of the episode until all evidence of disease had resolved.

Physicians and trained nurse interviewers used standard criteria in evaluating clinical symptoms as well as in determining resolution and new episodes of disease. Ears were examined with pneumatic otoscopy and tympanometry by the same group of physicians for the duration of the study. Infants were examined monthly after the initial diagnosis of OM until resolution of middle-ear disease. New episodes were defined after resolution of at least 30 days, with the unit of analysis being the child (avoiding problems of interdependence when the ear is used in the analysis).11

Feeding groups were defined as 1) exclusively breast milk-fed; 2) combined breast- and formula-fed; and 3) exclusively formula-fed. Maternal and paternal smoking history was defined for current smoking status at birth of index child and was reviewed retrospectively at 24 months of age (κ > .70). Number of cigarettes smoked per day was not determined. Day care contact by index children and their siblings was recorded at scheduled visits.

Laboratory Procedures

Nasopharyngeal cultures were obtained with a small rayon swab. Swabs were placed in transfer medium for laboratory processing using standard techniques. Collected specimens were cultured on trypticase soy agar with 5% sheep blood, chocolate agar, and MacConkey agar within 8 hours of collection. Bacteriology
procedures used for identification of *S. pneumoniae*, nontypeable *H. influenzae*, and *M. catarrhalis* are described extensively in previous reports from our laboratory.12–14

**Data Analysis**

Cumulative incidence was used to express rates of unilateral or bilateral OM episodes in the various feeding groups. Tests of association for categoric comparisons were expressed as relative risk (RR) and their appropriate 95% CI values. Because a large number of infants (N = 96) had only single acute episodes of OM in the first year, the distribution was highly skewed. A log-logistic regression model was used to test the relative effect of independent etiologic factors on first OM episodes.15 Additionally, Cox proportional hazard analyses16 \( h(t) = c(t)f(t) \) were performed to examine the role of breastfeeding and time-dependent factors (age at first pathogen colonization) in mediating OM episodes. The proportional hazard at time \( t \) is the probability of an episode occurring at time \( t \) given no event up to time \( t \) and for a specific value of a predictor variable (full or partially breastfed, formula). Covariates were entered in the chronologic sequence of assumed postnatal events (ie, feeding mode, age at colonization). The cumulative hazard functions for the two feeding groups are displayed graphically and are summarized as risk ratios in the results. SAS and SPSS/BMDP statistical software was used in the analysis.

**RESULTS**

Demographic and clinical characteristics of the study population are given in Table 2. Mean age of mothers was 29.6 ± 4.3 years (range, 19 to 42 years), with the majority of maternal guardians having completed a high school education (average education, 14 ± 2 years). The vast majority of study infants (99%) in the two suburban practices were Caucasian, and all infants were full term at birth. Despite problems of generalizing, the high compliance of this homogenous cohort is notable. Infants were enrolled between 1 and 6 weeks postnatally, 86% of infants completed 9 or more of the 13 scheduled visits over the 24 months of study follow-up. Home contact was maintained with the families, which minimized attrition rates (moving out of area, loss to follow-up).

In all, 58% of infants were exclusively breastfed at birth, 6% were combined breast- and formula-fed at birth, and 36% were exclusively formula-fed. The rate of exclusive breastfeeding in this infant cohort was ~30% at 3 months and 16% at 6 months.

As shown in Fig 1, the cumulative incidence of OM was ≤20% for the first 3 months of age, regardless of feeding mode. At 6 months, cumulative incidence of first episodes of OM remained <30% in infants exclusively breastfed (10/40), whereas cumulative incidence was >50% in infants formula-fed from birth (53/99). Peak incidence of OM rose earlier (3 to 6 months) in formula-fed infants compared with exclusively breastfed infants (6 to 12 months). Slightly more than 50% of infants exclusively breastfed for 6 months had first episodes of OM by the end of the first year (20/39), whereas 76% of exclusively formula-fed infants had first episodes of OM by 12 months of age (74/98).

The incidence of AOM and OME episodes is described separately in Fig 2 relative to changes in feeding mode and number of infants still being followed. Peak incidence of AOM and OME episodes was inversely related to rates of breastfeeding beyond 3 months of age. Rates of OM in breastfed infants partially supplemented with formula remained between rates reported for exclusively breast- and formula-fed infants during the first year. The effects of breastfeeding (duration, amount) on risk of AOM and OME episodes are examined further in the multivariate analyses reported later in “Results.”

Summarized in Fig 3, rates of colonization with potential middle-ear pathogens (any) were higher in infants currently formula-fed at 3 months of age (31.7%), 6 months (54.3%), and 12 months (48.9%) compared with infants exclusively breastfed (28.4%, 27.3%, and 50%). However, rates of colonization were only significantly different between the two exclusive feeding groups at 6 months of age (P = .003). Colonization rates in combined breast- and formula-fed infants were below or between rates observed in the exclusive feeding groups reported for the first 12 months (19.2%, 35.9%, 46.4%, respectively).

We summarized risk of first episodes of AOM and OME as it related to changes in feeding mode during the first 12 months of life (Table 3). Overall, first episodes of OM were elevated, but not significantly, in exclusively formula-fed infants compared with exclusively breastfed infants at 3 months of age (RR = 1.22, 95% CI: .97, 1.54); risk increased signifi-

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**TABLE 2.** Demographic and Clinical Characteristics of Infant Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>160 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>146 (48)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>302 (99)</td>
</tr>
<tr>
<td>African-American (and others)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>History of recurrent OM (more than three episodes)</strong></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>93 (31)</td>
</tr>
<tr>
<td>Paternal</td>
<td>58 (19)</td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
</tr>
<tr>
<td>Siblings*</td>
<td>110 (58)</td>
</tr>
<tr>
<td>24 Months</td>
<td></td>
</tr>
<tr>
<td>Siblings†</td>
<td>117 (59)</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Paternal</td>
<td>54 (18)</td>
</tr>
<tr>
<td><strong>Day care (outside house)</strong></td>
<td></td>
</tr>
<tr>
<td>12 Months</td>
<td></td>
</tr>
<tr>
<td>Sibling(s)‡</td>
<td>68 (35)</td>
</tr>
<tr>
<td>Infant</td>
<td>110 (36)</td>
</tr>
<tr>
<td>24 Months</td>
<td></td>
</tr>
<tr>
<td>Sibling(s)§</td>
<td>88 (44)</td>
</tr>
<tr>
<td>Infant</td>
<td>151 (49)</td>
</tr>
<tr>
<td><strong>Enteral feeding at entry</strong></td>
<td></td>
</tr>
<tr>
<td>Exclusive breast</td>
<td>178 (58)</td>
</tr>
<tr>
<td>Combined breast and formula</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Exclusive formula</td>
<td>110 (36)</td>
</tr>
</tbody>
</table>

* The percentage of infants for sibling history of recurrent OM at 12 months is based on the number of infants with siblings with available data (N = 191).
† The percentage of infants for sibling history of recurrent OM at 24 months is based on the number of infants with siblings with available data (N = 200).
‡ The percentage of infants with siblings in day care at 12 months is based on the number of infants with siblings with available data (N = 192).
§ The percentage of infants with siblings in day care at 24 months is based on the number of infants with siblings with available data (N = 201).
Significantly for the 6-month comparison in the exclusive feeding groups (RR = 1.59, 95% CI: 1.13, 2.24). Risk was marginally elevated in infants exclusively formula-fed versus those combined breast- and formula-fed at 6 months (RR = 1.28, 95% CI: 1.03, 1.59) and 12 months (RR = 1.30, 95% CI: .99, 1.70), respectively.

The putative beneficial effects of breastfeeding were somewhat clearer for acute episodes of disease. For short-term breastfeeding (3 months), first episodes of AOM were increased significantly in infants exclusively formula-fed compared with those infants exclusively breastfed from birth (RR = 1.39, 95% CI: 1.00, 1.94). For longer durations of exclusive breastfeeding (≥6 months), an approximately twofold elevated risk for AOM (RR = 1.82, 95% CI: 1.15, 2.90) and OME episodes (RR = 2.06, 95% CI: 1.01, 4.18) was observed. AOM, but not OME, episodes were significantly elevated in infants exclusively formula-fed compared with infants receiving breast milk combined with formula supplementation for 6 months. Recurrent episodes (at least two) of OM were also examined intensively in this infant cohort. Elevated risk for recurrent episodes of AOM (RR = 1.35, 95% CI: .82, 2.22) and OME (RR = 1.65, 95% CI: .67, 4.07) was noted in exclusively formula-fed compared with full or combined breast- and formula-fed infants, but the estimates were not significant.

Environmental exposures thought to intervene in the onset and recurrence of OM disease of infancy include infant and sibling day care outside the home, parental smoking, family history of OM, and other factors. A multivariate logistic regression including only significant risk factors from the univariate analyses and OM episodes from birth to 24 months is presented in Table 4. Formula-feeding remained the single most consistent predictor of OM episodes at 3, 6, and 12 months. An additional risk factor of note was day care contact (outside the home) by the index child (β = 1.08 ± .43; 95% CI: .22, 1.92). By 12 months...
of age, day care remained only marginally associated with elevated risk of OM episodes in index children ($\beta = .81 \pm .37$, 95% CI: .08, 1.54).

Similar risk estimates for AOM episodes were observed in exclusively formula-fed infants compared with breastfed infants at 3 months ($\beta = .99$, 95% CI: .11, 1.88), and 6 months ($\beta = 1.52$, 95% CI: .48, 2.56). Despite the silent nature of OME episodes, the protective effect of breastfeeding at 3, 6, and 12 months was remarkably similar to that observed for AOM in this study cohort. Day care (outside the home) of the index child appeared important, but of marginal sig-

| TABLE 3. Univariate Analysis of Feeding Modes and Risk of First Episode of Otitis Media During First 12 Months |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Risk Factors                         | Value           | 1st OM Disease  | 1st AOM         | 1st OME         |
|                                  |                 | RR              | RR              | RR              |
|                                  |                 | 95% CI          | 95% CI          | 95% CI          |
| Feeding mode during first 3 months | Exclusive formula* | 1.22            | 1.39            | 1.22            |
|                                  | Exclusive breast†  | 0.97, 1.54      | 1.00, 1.94      | 0.76, 1.95      |
| Feeding mode during first 6 months | Exclusive formula* | 1.59            | 1.82            | 2.06            |
|                                  | Exclusive breast†  | 1.13, 2.24      | 1.15, 2.90      | 1.01, 4.18      |
| Feeding mode during first 6 months | Exclusive formula* | 1.28            | 1.40            | 1.50            |
|                                  | Breast and formula‡ | 1.03, 1.59     | 1.04, 1.89      | 0.92, 2.43      |
| Feeding mode during first 12 months | Exclusive formula | 1.30            | 1.45            | 1.47            |
|                                  | Breast and formula‡ | 0.99, 1.70     | 0.99, 2.13      | 0.83, 2.59      |
| Feeding mode during first 12 months | Full formula§     | 1.24            | 1.35            | 1.37            |
|                                  | Breast and formula‡ | 0.96, 1.60     | 0.94, 1.94      | 0.81, 2.31      |

* Exclusively formula-fed for the respective months above included children who had only formula (feed = 2) for every month up to the last month in the analysis.
† Exclusively breast-fed for the respective months above included children who had only breast (feed = 1) for every month up to the last month in the analysis.
‡ Combined breast and formula-fed for the respective months above included children who had either breast (feed = 1) or both breast and formula (feed = 3) for every month up to the last month in the analysis.
§ Full formula-fed for the respective months above included children who were either formula (feed = 2) or weaned (feed = 4) at any time before or at the last month in the analysis.
Cumulative hazard function for onset of first OM: 6-month feeding.

Expressed as relative risk, after controlling for age at colonization, risk in exclusive formula-feeding infants increased substantially between 3 months (RR = 1.62, 95% CI: 1.12, 2.30) and 6 months of age (RR = 2.17, 95% CI: 1.36, 3.48). In addition, the results indicated that for each month pathogen colonization was delayed, a corresponding decrease in first OM episodes was observed.

**DISCUSSION**

The risk estimates presented for formula-feeding compared with breastfeeding in this study cohort are similar to those reported in several metaanalytic...
studies published recently. These studies indicate a beneficial effect of breastfeeding (even for short durations) on reducing AOM episodes in infancy. Day care outside the home was an important risk factor in our study and has been reported to be a significant risk factor for AOM in larger cohorts described in metaanalytic reports. Risk of recurrent AOM increases with number of contacts with other children; these contacts increase as children shift from family to day care centers outside the home. Additional investigation is needed to determine which factors (hygiene, size, duration) associated with day care attendance may be responsible for increased risk of otitis media onset in infancy.

The lack of information on dose exposures of infants to tobacco smoke makes interpretation of parental smoking risk more difficult. In the present study, maternal smoking appeared to be associated with increased risk of AOM and OME in infancy. No association between parental smoking and risk of OM episodes was found, however, when duration of breastfeeding, age at colonization with middle-ear pathogens, and day care contact outside the home were also considered in the multivariate logistic regression analyses. Our findings are consistent with those of other cohort studies published recently.

Selecting a causal model, when possible, may lead to clearer interpretation of scientific and clinical results than simply using data-driven analyses. Time dependence, as used in the proportional hazards causal model reported here, assumes that the status of the covariate (ie, age at pathogen colonization) may change with time, and that it has to be effective in the correct temporal sequence relative to disease; ie, its effect must precede the disease. Early age (≤3 months) of colonization with nontypeable H influenzae, S pneumoniae, or M catarrhalis has been associated with increased risk of OM episodes in infancy. The strong correlation \( r = .37, P < .001 \) between pathogen colonization rates and frequency of OM episodes found in the cohort is described more fully in a recent microbiology report by the coauthors (HF, LD, RW, et al). Early age at colonization (≤3 months) with middle-ear pathogens correlated with onset of OM episodes in infants <6 months of age. Alternatively, although our own extensive studies provide evidence that human milk has immunologic and nonimmunologic protective properties, data from our laboratories and elsewhere do not conclusively show whether breast milk is protective or whether components of formula-feeding are conducive to onset and recurrence of OM.

The protective effect of breastfeeding may be explained by several mechanisms, including exposure to infectious microorganisms, improved nutrition, and bioactive and antibacterial effects of human milk. The immunologic properties of human milk and other components that interfere with the attachment of bacterial pathogens to nasopharyngeal epithelial cells warrant additional study. Special emphasis needs to be given to age effects relative to duration of breastfeeding and onset of OM disease.

The results confirm the frequent nature of AOM and de novo OME and stress the necessity for clear, consistent definitions of the criteria for differentiating AOM and OME in epidemiologic research. Risk of AOM and OME was reduced significantly in infants exclusively breastfed until 6 months of age, after which breast milk was supplemented with other nutrients or discontinued. With the decline of exclusive breastfeeding and with increasing months of environmental exposures (day care, parental smoking), feeding group differences between 6 and 12 months were reduced. Nevertheless, increased risk for AOM and OME episodes during the first 2 years of life was identified with early pathogen colonization, day care outside the home, and not being breastfed.

The results clearly identify modifiable postnatal risk factors for AOM and OME in infancy. Reduction in colonization with middle-ear pathogens in infants ≤3 months of age requires closer examination. Encouraging home day care and breastfeeding for at least 3 months appear to be modifiable risk factors that significantly impact onset and duration of OM.

ACKNOWLEDGMENTS

This research was supported by National Institute of Child Health and Human Development Grant 19679.

We thank Elizabeth Griffiths, PhD, and Allen Leavens, MSc, for assistance in preparing the manuscript.

Fig 5. Cumulative hazard function for onset of first OM: 6-month feeding, \( h(t) = h_0(t) \exp\{-0.0999(t - 1)\} \) with increased risk of OM episodes in infancy. The results clearly identify modifiable postnatal risk factors for AOM and OME in infancy. Reducing in colonization with middle-ear pathogens in infants ≤3 months of age requires closer examination. Encouraging home day care and breastfeeding for at least 3 months appear to be modifiable risk factors that significantly impact onset and duration of OM.
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Pediatrics 1997;100;e7
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