Mannose-Binding Lectin and Upper Respiratory Tract Infections in Children and Adolescents

A Review

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Objective: To review the literature on mannose-binding lectin (MBL) polymorphisms and susceptibility for upper respiratory tract infection (URI) in children and adolescents.

Data Sources: We searched PubMed from 1966 and EMBASE from 1974 to July 2005, using the terms respiratory tract infection, respiratory infection, upper respiratory infection, MBL, and mannose-binding lectin.

Study Selection: Initially, 110 studies were identified. Two reviewers independently screened identified titles and abstracts. Potentially relevant studies were obtained and the full text examined. Inclusion criteria were human subjects, 18 years or younger, URI, and MBL polymorphisms. Seven of the initially identified studies met the inclusion criteria.

Data Extraction: Information was gathered for each study on study design, population, possible confounders, and outcomes measured.

Data Synthesis: Because there was significant heterogeneity between the identified studies, we had to describe the identified studies separately. The largest case-control studies (n = 3) as well as the cohort study (n = 1) suggest an association between MBL polymorphisms and URI, especially in young children. Results of the smaller studies (n = 3) are inconsistent.

Conclusions: The association between MBL polymorphisms and URI in children remains controversial. Large prospective cohort studies with regular documentation of URI and possible confounders such as atopy and environmental factors are required to establish the role of MBL polymorphisms in susceptibility for URI.

individuals also vary because of 3 major polymorphisms in the promoter region of the MBL gene (HL, PQ, and XY). These promoter polymorphisms influence transcription activity and synthesis of MBL.11 Polymorphisms in the MBL gene are very common, and low serum levels of MBL are found in 10% to 15% of white populations.11 This condition has been connected with increased general susceptibility to infectious diseases and to infection by specific pathogens such as Streptococcus pneumoniae, which is one of the most important pathogens causing URI.12-15 In this narrative review, we focused on the role of MBL polymorphisms in susceptibility for URI in children and adolescents.

**METHODS**

**DATA SOURCES**

We searched PubMed from 1966 and EMBASE from 1974 to July 2005, using the terms respiratory tract infection, respiratory infection, upper respiratory infection, MBL, and mannose-binding lectin to identify articles reporting on the association between polymorphisms of MBL and URI. In addition, a reference and related article search was performed.

**STUDY SELECTION**

Two reviewers independently screened identified titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. Discrepancies between reviewers were resolved by discussion. Criteria for inclusion in this survey were human subjects, 18 years or younger, URI, and MBL polymorphisms.

**DATA EXTRACTION AND SYNTHESIS**

Information was gathered for each study on study design, population, possible confounders, and outcomes measured. Because there was significant heterogeneity between the identified studies, pooling of the major outcomes was not possible. The results of the studies are therefore described separately.

Initially, 97 articles were identified with PubMed, whereas EMBASE revealed 13 studies that were not found on PubMed. Of these 110 studies, only 7 articles met the inclusion criteria (Figure).

Of the 7 included studies, 4 demonstrated a positive association between variant MBL alleles and URI and 3 articles did not find a positive association. The main characteristics of the studies are given in the Table. Various designs were used (ie, case-control [n = 5], cross-sectional survey [n = 1], and cohort [n = 1]). The age of the studied populations varied from birth to 18 years, and 2 studies only included young children (age <3 years). Because the heterogeneity between studies was large, we discuss each study separately.

Summerfield et al13 examined children attending a hospital and compared children who were admitted with infections (including URI) with children who were admitted as having various other diagnoses. The prevalence of variant alleles of the MBL gene in children with infections was twice that in children without infections. Increased susceptibility to infections was found in both heterozygotic and homozygotic children, but homozygotic children had more severe infections (including recurrent URI).

Koch et al16 investigated the effect of MBL polymorphisms on risk for acute respiratory tract infection in a population-based cohort of young children. The cohort was followed up weekly during a 2-year period for respiratory morbidity, and MBL genotypes were determined at the end of the study period. A 2-fold risk of acute respiratory tract infections was found in children with variant MBL alleles compared with children with normal alleles, but detailed analyses showed that this association was restricted to children aged 6 to 17 months.

Cedzynski et al17 compared the frequency of variant MBL alleles in children attending the hospital with recurrent respiratory tract infections and healthy controls. Children with recurrent respiratory tract infections had a 2 times higher risk of carrying variant alleles compared with healthy control children.

Garred et al18 compared the frequency of variant MBL alleles in patients suspected of immunodeficiency with healthy adults. Although the age of the study population exceeded 18 years (range, 2 months to 76.3 years), we decided to include this study because the median age of the study population was 57 months, with an interquartile range of 20 to 137 months. The frequency of heterozygotes for the variant alleles did not differ between patients and controls. The frequency of homozygotes, however, was higher in the patient group. They also found an association between homozygosity for MBL variants and severe recurrent otitis media and throat infections. The validity of the side outcome of URI can be argued because the study population comprised patients suspected of various immunodeficiencies. Nonetheless, it remains noteworthy that 5 of 20 MBL homozygotic patients were reported to have recurrent URI. With their repertoire of laboratory analyses, the authors could not identify 1 precipitating cofactor (ie, other immunodeficiency), except for a possible association with IgG subclass deficiency.

Three studies did not find an association between MBL polymorphisms and URI. Garred et al19 compared the MBL genotyping of children with recurrent otitis media, who
were admitted to the hospital for ventilating tubes and/or adenoidecotomy with healthy controls.\textsuperscript{18} The frequency of the \textit{B} allele did not differ between groups, but a trend was shown toward more homozygosity of the \textit{B} allele in the patient group.

Homèe et al\textsuperscript{19} studied the association between variant MBL alleles and episodes of acute otitis media in a survey of community-based, unselected children. No association was found with respect to the presence of variant MBL alleles and acute otitis media, recurrent acute otitis media, or age at first acute otitis media episode.

Finally, Ozbas-Gerceker et al\textsuperscript{20} compared variant alleles of MBL in children with recurrent otitis media with healthy controls. The frequency of the \textit{B} allele was found to be lower in children with recurrent otitis media compared with healthy controls, but the overall distribution of genotypes did not significantly differ these 2 groups.

### DIFFERENCES IN STUDY DESIGN

The 7 studies reviewed showed inconsistent results, which may be because of differences in study design, study population, and outcomes measured. Most of the identified studies were case-control studies, and it is known that measurement of exposure of the determinant (ie, MBL polymorphisms) leading to the disease or outcome (ie, URI) often is less accurate in case-control studies compared with cohort studies. Another problem with case-control studies is selecting the control group, which might lead to selection bias. Furthermore, only Koch et al\textsuperscript{16} adjusted for potential confounders such as age, sex, ethnicity, and calendar period.

Differences in study population such as genetic background, age, and number of subjects are potentially a major source of variation. In the studies by Ozbas-Gerceker et al,\textsuperscript{20} Cedzynski et al,\textsuperscript{7} and Garred et al,\textsuperscript{13} only white children were included. However, Summerfield et al,\textsuperscript{12} Koch et al,\textsuperscript{16} and Homèe et al\textsuperscript{19} studied children with different genetic backgrounds. Koch et al\textsuperscript{16} and Homèe et al\textsuperscript{19} included Greenlandic Eskimo, mixed-race, and white children. Upper respiratory tract infections including acute otitis media are known to occur earlier and more frequently among Eskimo children. In general, frequencies of variant MBL alleles differ among ethnic populations.

Age is another important characteristic of the study population in this setting, as it has been suggested that MBL is particularly important in children between ages 6 and 18 months. In that period, the adaptive system is still immature, and levels of maternally derived immunoglobulins are decreasing.\textsuperscript{8} This is confirmed by the study by Koch et al,\textsuperscript{16} which showed that MBL polymorphisms particularly influence the risk of acute respiratory tract infections in children aged 6 to 17 months, while

<table>
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<th>Source</th>
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<td>Summerfield \textit{et al}\textsuperscript{12} (London, England)</td>
<td>Case-control, hospital based</td>
<td>P: 345 children and adolescents admitted with infections; C: 272 children and adolescents admitted with other diagnoses (age, (18) y)</td>
<td>Frequency of MBL genotypes ((A, B, C,) and (D) allele)</td>
<td>Increased prevalence of (B, C,) and (D) allele in children and adolescents with infections, including URI (42.3% vs 23.5%); OR, 2.4 (95% CI, 1.4-4.0)</td>
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<td>Koch \textit{et al}\textsuperscript{16} (Sisimiut, Greenland)</td>
<td>Cohort, population based</td>
<td>P: 252 children in cohort (age, (&lt;2) y)</td>
<td>Risk of acute RTIs compared by MBL genotype</td>
<td>MBL insufficiency ((Xa/O + O/H)) associated with a 2.08-fold increased risk for acute RTIs (95% CI, 1.41-3.06); risk association largely restricted to those aged 6-17 months</td>
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<td>Cedzynski \textit{et al}\textsuperscript{17} (Lodz, Poland)</td>
<td>Case-control, hospital based</td>
<td>P: 335 children with recurrent RTI; C: 78 healthy children (age, 1-16 y)</td>
<td>Frequency of MBL genotypes ((A, B, C,) and (D) allele)</td>
<td>Increased proportion of (O/H) (OR, 0.001) in children and adolescents with recurrent RTIs</td>
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<td>Garred \textit{et al}\textsuperscript{13} (Copenhagen, Denmark)</td>
<td>Case-control, hospital based</td>
<td>P: 229 patients suspected for immunodeficiency; C: 123 healthy adults (age, 0-76 y; mean age, almost 5 y)</td>
<td>Frequency of MBL genotypes ((A, B, C,) and (D) allele)</td>
<td>Frequency of homozygosity for variant alleles in patients increased ((P = 0.0017)); variant alleles (B) and (D) associated with severe recurrent otitis media occurring with throat infections</td>
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<td>Garred \textit{et al}\textsuperscript{18} (Copenhagen, Denmark)</td>
<td>Case-control, hospital based</td>
<td>P: 89 children with otitis media (age unknown); C: 123 healthy adults</td>
<td>Frequency of MBL genotypes ((A) and (B) allele)</td>
<td>Frequency of (B) allele not different in children with recurrent otitis media ((P = 0.65))</td>
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<td>Homèe \textit{et al}\textsuperscript{19} (Nuuk, Greenland)</td>
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<td>P: 73 unselected children (age, 3-8 y)</td>
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<td>Presence of (B) or (D) allele not associated with recurrent acute otitis media or age at first acute otitis media episode</td>
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<td>Ozbas-Gerceker \textit{et al}\textsuperscript{20} (Ankara, Turkey)</td>
<td>Case-control, hospital based</td>
<td>P: 69 children with recurrent otitis media (age, (0-3) y); C: 100 healthy adults</td>
<td>Frequency of MBL genotypes ((A, B,) and (C) allele)</td>
<td>Frequency of (B) allele lower in children with recurrent otitis media (OR, 2.33; 95% CI, 1.06-5.11; (P = 0.03)); no difference in overall distribution of the genotypes ((P = 0.068))</td>
</tr>
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**Table. Summary of Studies on MBL Polymorphisms and URI in Children and Adolescents**

Abbreviations: \(A\) allele, normal, wild-type; \(B\) allele, single base pair substitution at codon 54; \(C\) allele, single base pair substitution at codon 57; CI, confidence interval; \(D\) allele, single base pair substitution at codon S2MBL; polymorphisms; MBL, mannose-binding lectin; OR, odds ratio; RTI, respiratory tract infection; URI, upper respiratory tract infection.
the effect is smaller in older children. The effect of age might explain the different results found by Homoe et al\textsuperscript{16} because in their study children younger than 3 years were excluded. The number of children studied also varied between the studies. A positive association between MBL polymorphisms and URI was found in the larger studies, whereas the smaller studies did not find an effect, which might reflect a power problem.

In our opinion, the study by Koch et al\textsuperscript{16} is most valuable because it is a large prospective cohort study with regular documentation of infections. Nevertheless, it is important to realize that they studied mostly Eskimo children. Their specific genetic background and a priori high risk for URI make results hard to generalize to white children. Finally, it should be noted that publication bias cannot be precluded because registers for nonexperimental studies have not yet been created. Differing outcomes measured by the included studies might be another explanation of the different study results. One study measured severity of URI\textsuperscript{11,16} and the other studies measured risk of recurrence of infection.\textsuperscript{17-20}

We addressed URI instead of the individual diseases like common colds, rhinosinusitis, pharyngotonsillitis, and otitis media. In 4 of the included studies only otitis media was studied, whereas in the other studies respiratory tract infections in general were studied. The effect of MBL polymorphisms may differ regarding different clinical manifestations or various microbial agents. However, the pathogenesis of different URI is very similar and often associated.

CIRCUMSTANTIAL EVIDENCE

There is a strong association between MBL polymorphisms and MBL serum levels.\textsuperscript{9-11} However, like an acute-phase protein, MBL serum levels may rise under stress.\textsuperscript{21} Moreover, genotyping becomes more and more easily accessible, and genotyping costs are declining. Therefore, in our opinion, genotyping is preferable in future studies.

In this review we included only MBL genotyping studies, but studies focusing on MBL levels in serum provide additional results. Aittoniemi et al\textsuperscript{22} determined MBL serum levels in children with increased susceptibility to infections, mostly respiratory tract infections. Levels of MBL serum did not differ between these children and the general Finnish population, but MBL deficiency seemed to be manifested in combination with other immunodeficiencies. The same observation was seen in a recent cohort study by Thorarinsdottir et al\textsuperscript{23} in which MBL serum did not differ between children and the general population, whereas Dahl et al\textsuperscript{24} found a higher frequency of MBL variants resulting in low serum levels among healthy subjects.

The ideal study to establish the role of MBL polymorphisms in susceptibility for URI in children was a large long-term prospective cohort study with repeated documentation of respiratory tract infections and possible confounders such as atopy and other genetic and environmental factors.

Inconsistent results were found in the literature regarding MBL polymorphisms and susceptibility for URI in children. Case-control studies including larger numbers of children as well as a cohort study suggest an association between MBL polymorphisms and susceptibility for URI in children. Other studies, however, did not find an association between MBL polymorphisms and URI.

The critical role of MBL polymorphisms in susceptibility for URI in children would be a large long-term prospective cohort study with repeated documentation of respiratory tract infections and possible confounders such as atopy and other genetic and environmental factors.

Submitted for Publication: September 28, 2005; final revision received December 5, 2005; accepted January 3, 2006.

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Financial Disclosure: None.

REFERENCES

5. Rovers M, Haggard M, Gannon M, Koeppen-Schomerus G, Plomin R. Heritabil-

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ity of symptom domains in otitis media: a longitudinal study of 1,373 twin pairs. 