pneumonia, we are unable to optimize strategies for antiviral and antibiotic use. For example, in a severe pandemic there would probably be too few hospital beds to treat all patients needing systemic antibiotics. Many physicians would probably treat with oral antibiotics on an outpatient basis, and they would probably also prescribe antibiotics for persons who were in the early stages of clinical influenza but who did not have pneumonia. Knowledge of the pathogenesis and natural history of severe influenza pneumonia and its interrelationship with bacterial pneumonia is therefore essential. Although it is reassuring that we now have vaccines against 2 of the 3 major bacterial causes of secondary pneumonias studied during 1918–1919, current vaccination policies might leave many persons in the general population unprotected. We support the conclusions of Brundage and Shanks, adding that much additional research is needed to continually refine and update our preparedness for an influenza pandemic.

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References

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CORRESPONDENCE • JID 2007;196 (1 December) • 1719

Comments on “Cytomegalovirus (CMV)–Encoded UL144 (Truncated Tumor Necrosis Factor Receptor) and Outcome of Congenital CMV Infection”

To the Editor—We read with interest the article by Arav-Boger et al. concerning human cytomegalovirus (HCMV) UL144 gene polymorphism in HCMV congenital infections [1]. The recently discovered HCMV UL144 protein is a tumor necrosis factor–like receptor [2]. Among HCMV clinical strains, the UL144 gene exhibits complete identity in transmembrane and cytoplasmic domains, although high-sequence variation in the ectodomains allowed Lurain et al. to identify 3 major genotypes (A, B, and C) [3]. The association between the genotypes of this potential virulent gene and HCMV disease has been studied.

Arav-Boger et al. [1] identified the UL144 genotypes in 56 cases of congenital infection diagnosed in Italy; the outcomes included 25 terminations of pregnancy, 1 intrauterine death, and 30 deliveries. The classification of asymptomatic and symptomatic neonates was based on an extensive examination of live-born neonates and on histological data regarding terminations of pregnancy. All 25 aborted fetuses were classified as belonging to the symptomatic group, either because of potent organ disease or because of the presence of disseminated infection. In their study, Arav-Boger et al. reported an association between genotype C and symptomatic disease in newborns ($P = 0.05$) and between genotype C and termination of pregnancy ($P = 0.03$).

We had previously reported the distribution of the UL144 polymorphism gene in 36 cases of documented CMV congenital infection in a French population; however, we did not find any association between genotype and the outcome of CMV congenital infection [4]. Arav-Boger et al. obviously misunderstood some aspects of our study, and we would like to clarify the significance of our findings as well as present additional data. In our population, there were 23 terminations of pregnancy and 13 deliveries. Of the 13 newborns, 9 were asymptomatic, and 4 were symptomatic, according to extensive examination at birth. The 23 aborted fetuses were classified, according to ultrasound data, as severely symptomatic (i.e., having only 1 extra cerebral feature) in 21 cases and as nonseverely symptomatic (i.e., having only 1 extra cerebral feature) in 2 cases. We did not base the classification of aborted fetuses on histological data because the aforementioned results were not available for all cases and because, in our experience, disseminated infection is found frequently in aborted infected fetuses, even in those without features detected by ultrasound or magnetic-resonance imaging, and we think that the presence of disseminated infection at the histological level, without organ disease, is not a good indicator of whether these fetuses would have been symptomatic at birth or afterward. In our study, there were 12 cases of infection with the C genotype—9 (75%) had a bad outcome (7 terminations of pregnancy with severely symptomatic fetuses and 2 symptomatic neonates) and 3 (25%) were asymptomatic neonates. Arav-Boger et al. described 7 cases of C genotype infection—6 in aborted fetuses and 1 a case of intrauterine death. All 7 of these cases were classified as symptomatic because of either obvious organ involvement at histological examination (5 cases) or the presence of disseminated infection (2 cases) (the classification of these last 2 cases could be discussed as developed above).

To better compare our results with those of Arav-Boger et al., we calculated the association between genotypes and termination of pregnancy, as shown in table 1; we could not find any correlation between genotype C and termination of pregnancy in the population that we studied. We compared viral loads (obtained by in-house real-time polymerase chain
reaction [5]) in amniotic fluids of the different UL144 genotypes and found that the median viral loads were not statistically different for genotypes A, B, and C: their medians were 7.00 (range 2.5–7.95), 6.97 (range 5.27–10.3), and 7.04 (range 3.21–8.59) log10 copies/mL, respectively (as also described by Arav-Boger et al.).

Therefore, in the population that we studied, UL144 polymorphism was associated neither with the outcome of congenital infection nor with viral-load levels in amniotic fluid. Moreover, the role played by UL144 protein has been partially elucidated recently: (1) The UL144 protein inhibits T cell proliferation by binding to the B and T lymphocyte attenuator, probably via its ectodomain cystein-rich domain 1; however, despite genetic polymorphism in this domain, this activity was similar within all genotypes studied (A, B, and C) [6]. (2) The UL144 protein activates NFkB, thereby helping the virus to evade the host immune system; this property was the same for 2 of the genotypes studied—A and B [7]. This finding (i.e., that UL144 variants have the same in vitro activity) would be consistent with a similar pathogenicity in vivo.

### References


Potential conflicts of interest: none reported.

Informed consent was obtained from all patients’ parents and the guidelines of the French Department of Health were followed in conducting this study.

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### Table 1. Association between UL144 genotypes and termination of pregnancy.

<table>
<thead>
<tr>
<th>Genotype (n)</th>
<th>Termination, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n/100)</td>
</tr>
<tr>
<td>B (n/13)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Non-B (n/23)</td>
<td>15 (65)</td>
</tr>
<tr>
<td>C (n/12)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Non-C (n/24)</td>
<td>16 (67)</td>
</tr>
</tbody>
</table>

**NOTE.** P values were not significant.