Neonatal Cytomegalovirus Blood Load and Risk of Sequelae in Symptomatic and Asymptomatic Congenitally Infected Newborns

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ABSTRACT

OBJECTIVE. Human cytomegalovirus (CMV) is a ubiquitous human-specific DNA virus and is the main cause of congenital virus infection in developed countries leading to psychomotor impairment and deafness. Diagnostic techniques for CMV detection have greatly improved during recent years with the advent of sophisticated serological and virological methods. The aim of the present study was to assess the diagnostic and prognostic value of detection and quantification of virus in neonatal blood samples of symptomatic and asymptomatic newborns with CMV congenital infection.

METHODS. Between January 1997 and December 2003, we studied 99 newborns who were born to women with primary, recurrent, and undefined CMV infection during pregnancy. CMV congenital infection was identified by isolation of the virus in urine within the second week of life. Fifty-eight of 99 infants were infected and were assessed clinically for disease in the newborn period and classified as having symptomatic or asymptomatic infection on the basis of physical, instrumental, and laboratory findings. The infants were followed up from birth according to a protocol of the tertiary NICU at the University of Bologna in a prospective study of long-term sequelae of congenital infection. Forty-seven blood samples were obtained from 47 infants in the neonatal period: 34 were examined for pp65 antigenemia test and 44 for qualitative and quantitative polymerase chain reaction (PCR and qPCR). Sequelae at 12 months were evaluated in a group of 50 infants.

RESULTS. Antigenemia was positive in only 10 of 34 samples of infected newborns (29.4% sensitivity). PCR was performed in 44 samples of infected newborns and was positive in all (100% sensitivity). qPCR showed a finding of ≥100 copies per 10^5 of polymorphonuclear leukocytes (PMNLs) in 39 of 44 samples; in the other 5 cases, the number of copies per 10^5 PMNLs was <100. Between symptomatic and asymptomatic newborns, the mean values of viral blood load determined by
qPCR turned out to be significantly higher in symptomatic newborns. Mean values of neonatal viral load were statistically higher in newborns who developed sequelae than in those who did not. Of 20 children with a neonatal viral load of <1000 copies per 10⁵ PMNLs, 19 did not develop sequelae (negative predictive value: 95%), whereas 2 of 3 with a viral blood load of >10 000 copies did develop sequelae.

CONCLUSIONS. Different viremia value ranges are correlated to a different risk of sequelae: ~70% sequelae were found in newborns with a qPCR higher than 10 000 copies per 10⁵ PMNLs. Low neonatal viral blood load detected by pp65 antigenemia test and qPCR was highly predictive of absence of sequelae: DNAemia <1000 copies per 10⁵ PMNLs has a negative predictive value of 95%. As an independent predictive factor of outcome, neonatal viremia is another useful element for neonatal counseling and therapeutic choices in symptomatic and asymptomatic newborns.

HUMAN CYTOMEGALOVIRUS (CMV) is a ubiquitous human-specific DNA virus that belongs to the Herpesviridae family. More than 90% of primary infections are asymptomatic in healthy adults and children, but CMV is an important cause of morbidity and mortality in immunocompromised individuals, pregnant women, newborns, and preterm infants.¹

Diagnostic techniques for CMV detection have greatly improved during recent years with the advent of sophisticated serological and virological methods, but the significance and usefulness of different assays depend on patient categories. Quantitative virological methods (viremia, antigenemia, and DNAemia) are used to predict and monitor CMV disease, institute preemptive therapy, and monitor antiviral treatments in immunocompromised patients such as transplant recipients and those with AIDS.² In pregnant women, CMV isolation and/or detection of viral DNA by polymerase chain reaction (PCR) in amniotic fluid is useful in defining the risk for fetal infection.³,⁴

The diagnosis of congenital CMV is best accomplished by viral culture of saliva or urine or by PCR testing of either specimen within the first 2 weeks of life.⁶ Congenitally infected infants are asymptomatic at birth in ~85% to 90% of cases.⁹ Infection in symptomatic infants ranges from mild to severe disseminated life-threatening disease resulting in up to 20% perinatal mortality.¹⁰ Up to 80% of symptomatic newborns will exhibit sequelae such as mental retardation, cerebral palsy, seizures, visual defects, and sensorineural hearing loss. In addition, 8% to 15% of infants who are asymptomatic at birth will later develop complications, mainly neurodevelopmental defects and deafness.¹¹,¹²

Symptoms at birth therefore have a negative prognostic significance. Studies that have been performed to define the prognostic value of clinical, laboratory, and instrumental findings in symptomatic infected newborns have reported contradictory findings.¹⁰,¹³–¹⁶ Moreover, insufficient data are available on the possibility of an early definition of outcome in the larger group of asymptomatic newborns.

The identification of ≥1 prognostic markers in newborns who have congenital CMV infection and are at increased risk for sequelae could allow careful monitoring to institute prompt rehabilitative and therapeutic strategies to curb subsequent damage. The aim of the present study was to assess the diagnostic and prognostic value of detection and quantification of virus in neonatal blood samples of symptomatic and asymptomatic newborns with congenital CMV infection.

METHODS

Study Population

Between January 1997 and December 2003, we studied 99 newborns who were born to women who were referred to us by gynecologists as affected by primary, recurrent, and undefined CMV infection during pregnancy. Women who had anti-CMV immunoglobulin (Ig) G of low avidity or who seroconverted to CMV IgG positivity were classified as undergoing primary infection. Those with anti-CMV IgG of high avidity and blot-confirmed IgM positivity were classified as having a recurrent (reactivated) infection. Finally, doubtful serological results were classified as undefined.

Congenital CMV infection was identified by isolation of the virus in urine within the second week of life. In the first 2 years of our study, we conducted viruria and viremia determinations at the same time, and the next viremia determination was performed only when viruria was positive.

Fifty-eight of 99 infants were infected and were followed up from birth according to a protocol of the tertiary NICU at the University of Bologna in a prospective study of long-term sequelae of congenital infection. Of the 58 infected newborns, 52 were from mothers who developed a primary CMV infection during pregnancy: 17 were symptomatic and 35 were asymptomatic at birth. Four newborns were delivered from mothers who developed a recurrent CMV infection, and all were found to be symptomatic. The 2 remaining newborns were from mothers with undefined infection in pregnancy: 1 was symptomatic, and 1 asymptomatic.

All children were assessed clinically for disease in the newborn period and were classified as having symptomatic or asymptomatic infection on the basis of physical, instrumental, and laboratory findings. Newborns were considered symptomatic when they showed ≥1 of the following findings: signs and symptoms of systemic involvement such as intracutaneous growth retardation, hep-
atrophymegaly, skin petechiae/purpura, thrombocyto-
penia (platelet count: <100 000/mm³), jaundice with
direct bilirubin (>3 mg/dL), alanine aminotransferase
(ALT) elevation (>80 U/L), pneumonia, neurologic in-
volve ment (microcephaly, lethargy/hypotonia, poor
sucking, and seizures), and sensorineural defects (chori-
oretinitis and deafness), and CMV-associated patterns at
neuroimaging (abnormal periventricular hyperechoge-
nicity, intracranial calcifications, ventriculomegaly, hy-
perechogenicity of lenticolo-striatal vessels, etc.)¹⁷

All infants were followed up at birth, at 1, 3, 6, 12,
and 18 months of life, and then annually up to school
age. Follow-up included clinical evaluation, neurodevel-
opmental and psychointellectual assessment, cranial ul-
sound, cerebral computed tomography (in case of
doubts at sonographic examination) and MRI (in case of
neurologic symptoms or pathologic ultrasound), fundu-
scopic examination, and audiological assessment. When
pathologic features were detected, children were seen
more frequently.

Of 58 newborns enrolled, 2 with severe congenital
symptomatic CMV infection (1 with aortic arch throm-
bosis¹⁸ and 1 with severe hydrops) died during the neo-
natal period and 2 were lost to follow-up. Sequelae at 12
months of life were evaluated in 50 of 58 infants (15
with and 35 without symptoms at birth) because 4 chil-
dren were younger than 1 year (Fig 1).

Forty-seven blood samples were obtained from 47
infected children in the neonatal period. Of 47 polymor-
phonuclear leukocyte (PMNL) samples, 34 were exam-
ined for pp65 antigenemia test and 44 for qualitative
PCR and quantitative PCR (qPCR). Twenty neonatal
blood samples were obtained for determination of pp65
antigenemia and PCR tests from 20 infants who were
found not to be infected as shown by negative virus
isolation from urine. This group was followed up and
served as a control group.

Virological Tests

CMV Isolation

Human embryo fibroblasts were grown in Eagle’s mini-
mal essential medium with 10% fetal calf serum. For
virus isolation, the shell vial procedure was used.¹⁹ The
inoculated cells were fixed 24 to 48 hours after inocu-
lation and were stained by an indirect immunofluores-
cence assay with a monoclonal antibody that reacts with
the CMV IE1 and EA gene product (E13 + 2A2; Argene,
Varilhes, France).

Antigenemia

Blood samples were collected in EDTA-treated tubes.
PMNLs were separated using a standard dextran sedi-
mentation procedure. An aliquot of 2 × 10⁵ PMNLs was
spotted onto a slide for antigenemia assay as described
originally by van der Bij et al²⁰ and modified by Revello
et al.²¹ and indirect immunofluorescence was performed
using a pool of 2 monoclonal antibodies specific for CMV
pp65 (1C3 and AYM-1; Argene). Results were expressed
as the number of positive cells per 2 × 10⁵ PMNLs.

DNAemia

Two aliquots of 10⁶ PMNLs were frozen at −80°C before
subsequent PCR studies.

PCR

CMV-DNA was extracted from aliquots of 1 × 10⁶
PMNLs by CMV-Ibridoquant Extraction Kit (Bioline,
Turin, Italy). Nested PCR was performed for amplifica-
tion of a highly conserved region of the viral genome
(major immediate-early) using 2 primer sets described
elsewhere.²² PCR products were separated by electro-
phoresis on a 2% Nusieve-Seakem (2:1) gel (FMC Bio-
products, Rockland, ME) and visualized by transillumi-
nation. The sample was regarded as positive when a
band corresponding to a 110-bp DNA fragment was de-
tected. For excluding false-positive results owing to con-
tamination, 4 samples that contained the reaction mix-
ture but no target DNA were processed for each PCR
batch. All samples that contained no target DNA yielded
negative results.

qPCR

Quantitative assessment of the CMV DNA load was per-
formed with the COBAS AMPLICOR CMV MONITOR
Test (Roche Diagnostics, Branchburg, NJ). DNA was ex-
tracted from 10⁶ PMNLs that had been resuspended in
200 µL of phosphate-buffered saline. From this material,
50 µL of processed specimen was loaded into the COBAS
AMPLICOR instrument. Nucleic acid amplification and
detection proceeded in an automated manner. The re-
results of the PCR assay were reported as number of DNA
copies per 10⁵ PMNLs. One CMV low-positive control
(mean value: 3.79 copies per 10⁵ PMNLs; SD: 0.62), 1
CMV high-positive control (mean value: 4.56 copies per
10⁴ PMNLs; SD: 0.65), and 1 CMV negative control were
processed with each batch sample. The limit of detection
of this quantitative assay is 120 copies of CMV DNA per
10⁶ cells.

The blood samples were tested during the neonatal
period of each patient in routine laboratory activity. The
laboratory personnel who undertook molecular testing
were aware of the derivation and outcome of the infants
studied.

Clinical Examinations

Clinical examinations that were conducted at birth, at 1,
3, 6, 12, and 18 months of age, and annually thereafter
included measurement of anthropometric parameters
(weight, length, and head circumference) and assess-
ment of the relative percentiles.
Psychomotor and Neurodevelopmental Assessment
Neurologic assessment and the Brunet-Lezine test (which includes 4 subscales for evaluation of posture, coordination, speech, and socialization) for children at 3, 6, 12, 18, and 24 months of age and the Stanford Binet L-M Intelligence Scale (Terman Merrill revision) for older children were performed. The tests were always administered by the same investigators.

Audiological Assessment
An audiological evaluation was performed at birth and at 6 and 12 months of age and annually until school age. Brainstem evoked responses (BSERs) were used to assess audiological function during the first year of life. Behavioral audiometry was performed thereafter. Middle-ear disorder was excluded by tympanometry.

Visual Evaluation
Fundus examination was undertaken after topical ocu-lopelagic administration in the neonatal period and at 6 and 12 months of life.

Cranial Ultrasound Examination
Cranial ultrasound examinations were performed at birth and at 1, 3, and 6 months age by the same investigators (Gina Ancora, MD, and Fabrizio Sandri, MD), using an Esaote AU5 (Esaote Biomedica, Genoa, Italy) with a 5- to 7.5-MHz sector probe. Coronal and sagittal views were collected at different times.

Statistical Analysis
The statistical significance of the associations between the diagnostic tests and symptoms and/or sequelae in the newborns was determined using Fisher’s exact test or the $\chi^2$ test for trend (when appropriate). The comparison of the mean values of quantitative DNAemia was statistically assessed (after log transformation) by means of Student’s $t$ test for independent samples. A 2-tailed $P < .05$ was considered statistically significant. The sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of the tests were also assessed.
RESULTS

The derivation of the final study cohort, consisting of infants who were followed up for up to 12 months, is shown in Fig 1. Fifty-eight children with congenital CMV infection were followed up from the neonatal period: 24 (41.4%) boys and 34 (58.6%) girls. The mortality rate was 3.4% (2 of 58 congenitally infected). Twenty-two (37.9%) of the 58 newborns had symptomatic infection; their clinical, laboratory, and instrumental findings are summarized in Table 1.

Results of virological assays that were performed in the neonatal period are shown in Table 2. Antigenemia was performed in 34 samples from CMV-infected newborns, and positive results were detected in only 10 (29.4% sensitivity). Qualitative PCR was performed in 44 samples and was positive in all (100% sensitivity). All 20 congenitally uninfected newborns were negative for CMV DNA and for pp65 antigenemia test; therefore, these methods showed 100% specificity.

qPCR showed a finding of ≥100 copies per 10⁵ PMNLs in 39 of 44 samples (22 asymptomatic and 17 symptomatic). In the other 5 cases, the number of copies per 10⁵ PMNLs was <100, 4 of which were without and 1 of which was with symptoms.

Between symptomatic and asymptomatic newborns, the mean values of viral blood load determined by qPCR turned out to be significantly higher in symptomatic newborns (P = .020). Considering symptomatic only those newborns with clinical evidence of congenital CMV infection, thereby excluding infants with only isolated transient changes in laboratory or instrumental findings (ALT of >80 U/L, thrombocytopenia, hyper-echogenicity of lenticolo-striatal vessels), the differences in viral blood load between newborns with and without symptoms became more evident (P < .001; 95% confidence interval of the difference between the 2 means: 0.36–1.12).

The average duration of follow-up was 18 months. The incidence of sequelae was determined in the group of 50 infants who were followed for >12 months, 13 (26%) of whom developed sequelae induced by congenital CMV infection (Fig 1).

Twelve (80%) of 15 symptomatic newborns developed sequelae (Fig 1), with delayed psychomotor development and/or neurologic deficits and sensorineural hearing loss in 6 (50%) infants, 3 with severe bilateral deafness (BSER value ≥71 dB). Two (16.6%) of 12 infants presented only mild monolateral hearing loss (BSER value between 21 and 45 dB), whereas sequelae were confined to delayed psychomotor development and/or neurologic deficits in 4 (33.3%). Of the 35 newborns with asymptomatic CMV infection and a follow-up of at least 12 months (Fig 1), only 1 (2.9%) developed sequelae that consisted of hearing loss and hypertonia of the lower limbs. Of the 20 uninfected newborns in the control group, 16 had a clinical follow-up of at least 12 months, and none developed sequelae.

Of the 50 infants with a follow-up ≥12 months, 31 were tested for pp65 antigenemia and 37 underwent qPCR determination (Table 3). The mean value of neonatal blood viral load determined by qPCR was significantly higher in newborns who developed sequelae (P < .001), and the pp65 antigenemia test was more frequently positive in newborns who developed sequelae (P = .043; Table 3).

Figure 2 shows the significant association between neonatal blood viral load determined with qPCR and the development of sequelae at 12 months of age (test for trend, P = .002). None of the 4 children with CMV viral load <100 copies per 10⁵ PMNLs developed sequelae. One of 16 children with viral blood load between 100 and 1000, 7 of 14 with viral load between 1000 and 10 000, and 2 of 3 with viral blood load >10 000 copies developed sequelae.

The prognostic value of virus quantification in the blood of newborns with CMV congenital infection evaluated in the neonatal period is shown in Table 4. At a
cutoff point of at least 1000 copies per 10^5 PMNLs, among the 17 samples with neonatal viral blood load ≥1000, only 9 newborns developed sequelae (PPV: 53%). Only 1 of the 20 children with neonatal viral blood load <1000 copies per 10^5 PMNLs developed sequelae (NPV: 95%). The samples that were collected from this child had a value very near the cutoff point of 1000 (960 copies per 10^5 PMNLs). We obtained similar results with the pp65 antigenemia test because only 2 of 22 newborns with a negative determination developed sequelae (NPV: 91%).

**DISCUSSION**

Vertical transmission of CMV is the most common cause of congenital viral infection in developed countries (0.3%–2% of all live births, 1.1% in Bologna; unpublished data) and the leading nongenetic cause of sensorineural hearing loss. At birth, it is essential to use appropriate tests for the diagnosis of congenital CMV infection. The gold standard method is virus isolation from urine/saliva in the first 2 weeks of life because subsequent virus excretion may represent neonatal infection acquired in the birth canal or after exposure to breast milk. The determination of DNA in blood by PCR at birth seems to be as sensitive and specific as virus recovery from urine for diagnosis of congenital CMV infection. Negative results by these tests rule out congenital CMV infection, and no additional investigations are required.

CMV-infected newborns must undergo additional clinical, laboratory, and instrumental evaluation to identify those who are symptomatic. The presence of symptoms at birth strongly conditions the treatment and long-term outcome of infected infants. Nevertheless, the prognostic significance of single clinical, laboratory, and instrumental findings is limited.
instrumental findings observed in the neonatal period remains unsettled. Prognostic indicators for the larger group of asymptomatic CMV-infected children are lacking, so there are few objective elements to support neonatal counseling, with a high risk for poor family compliance at follow-up.

Our study investigated the diagnostic and prognostic significance of neonatal virological tests (pp65 antigenemia and DNAemia) in relation to psychomotor sequelae and hearing loss in symptomatic and asymptomatic congenitally CMV-infected newborns. In 1995, Nelson et al\(^\text{26}\) reported the detection of CMV DNA in the serum of 18 (100%) of 18 infants with symptomatic congenital CMV infection against none of the 32 control subjects. Revello et al\(^\text{27}\) investigated the diagnostic and prognostic value of CMV load at birth determined by different assays in the blood of 41 newborns with congenital infection and 34 uninfected newborns. Sensitivities of CMV DNAemia determination were 100%, whereas specificity was 100% for all assays.

We found the same results for qualitative PCR performed on PMNLs, with a positive determination in all 44 samples of infected newborns (100% sensitivity) and negative in 20 of 20 uninfected newborns in the control group (100% specificity). Similar results were found for the pp65 antigenemia test as regards specificity (100%), whereas the statistical value of sensitivity was very low (29.4%), in agreement with other authors.\(^\text{27}\)

We found that the neonatal viral blood load in symptomatic newborns (pp65 antigenemia and DNAemia) tended to be higher but did not reach statistical significance. However, we failed to find a correlation between viremia and symptoms from the reticuloendothelial system, including isolated elevated levels of ALT and thrombocytopenia or hyperechogenic lenticulo-striatal vessels deemed nonspecific sign.\(^\text{28}\) Considering only newborns with clinical evidence of CMV infection, the differences in viral blood load between newborns with and without symptoms became statistically significant.

A report by Rivera et al\(^\text{16}\) demonstrated that a high viral load in early infancy, expressed by a high amount of virus in urine, is highly predictive of audiological impairment. Finding CMV in blood indicates an active viral replication with ongoing dissemination, but its prognostic role in congenital infection has not been defined.

Our study disclosed that DNAemia performed at birth is significantly higher in newborns who went on to develop sequelae than in infants with a good outcome. Different DNAemia value ranges were correlated to a different risk of sequelae: none for qPCR <100 copies per 10⁵ PMNLs values and ~70% sequelae in newborns with qPCR higher than 10 000 copies per 10⁵ PMNLs.

Considering a cutoff point of 1000 copies per 10⁵ PMNLs in our population, we selected a group of newborns who had DNAemia <1000 and were at very low risk for sequelae (NPV: 95%). Only 1 infant in this group developed sequelae that consisted of neurodevelopmental retardation and late-onset hearing loss, but his DNAemia at birth had been only slightly below the cutoff. In addition, another DNAemia >10 000 copies at 12 months of follow-up did not have any sequelae. This finding is difficult to interpret and may result from late-onset sequelae.

Our study presents 1 of the largest cohorts of CMV-infected children acquired prospectively, but the sample distribution in terms of different intervals of viral blood load reduces the number of infants for each interval and awaits confirmation in larger series. The median value of pp65 antigenemia was significantly higher in the group of newborns who developed sequelae, as shown in Table 4. However, its scant diagnostic utility, the inherent variability resulting from the lack of standardization, the need for immediate processing of samples after collection, and the subjective nature of quantification discourage its use as a diagnostic tool for congenitally infected newborns.\(^\text{2}\)

To our knowledge, this is the first study to have assessed the prognostic significance of virological tests on blood samples (pp65 antigenemia and qPCR) from symptomatic and asymptomatic congenitally CMV-infected newborns. As in pregnancy, viral markers are

| TABLE 4 | Sensitivity, Specificity, PPV, and NPV of Neonatal pp65 Antigenemia and DNAemia (Cutoff Point 10³ Copies per 10⁵ PMNLs) With Regard to the Presence or Absence of CMV Sequelae at 12 Months of Life |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CMV Sequelae | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
| Yes | No |
| pp65 antigenemia (no. of pp65-positive cells per 2 × 10⁵ PMNLs) | | | | |
| Positive | 66.6 | 80 | 44.4 | 91 |
| Negative | 44.4 | 91 | 66.6 |
| Total | 31 | 91 | 66.6 |
| qPCR (no. of copies per 10³ PMNLs) | | | | |
| ≥10³ | 90 | 70.4 | 53 | 95 |
| <10³ | 70.4 | 53 | 90 |
| Total | 37 | 95 | 70.4 |

\(^a\) Fisher’s exact test.
very useful for neonatal counseling. Predicting neonatal outcome and the subsequent appearance of sequelae has undoubted advantages: (1) it will decrease the family’s anxiety if the predictive factors of good outcome are present; and (2) it stratifies patients who are at different risks for sequelae, modulating the follow-up steps and permitting early rehabilitative and/or therapeutic intervention to minimize long-term damage.

In agreement with Bradford et al., treatment decisions currently cannot be based solely on the presence of high CMV blood viral load at birth. However, this finding could identify the population in greatest need of antiviral therapy, whereas a low viral load may save the clinician from administering unnecessary treatments.

ACKNOWLEDGMENTS
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ERRATA


Two errors occurred in the AAP Policy Statement “Promotion of Healthy Weight-Control Practices in Young Athletes” that was published in the December 2005 issue of Pediatrics (2005;116:1557–1564; doi:10.1542/peds.2005-2314). Figure 1 was inadvertently omitted. Also, under recommendation 5, within the brackets in the third sentence, Figure 1 should have been cited instead of Table 3. The reader is directed to http://aappolicy.aappublications.org/cgi/reprint/pediatrics;116/6/1557 for an updated version.

doi:10.1542/peds.2006-0452


An error appeared in the article by Lanari et al, titled “Neonatal Cytomegalovirus Blood Load and Risk of Sequelae in Symptomatic and Asymptomatic Congenitally Infected Newborns” that was published in the January 2006 issue of Pediatrics Electronic Pages (2006;117:e76–e83; doi:10.1542/peds.2005-0629). On page e79, Figure 1, in the text box to the right of 58 enrolled, it reads “4 deaths.” It should read “2 lost and 2 deaths.”

doi:10.1542/peds.2006-0420


An error appeared in the article by Wennberg et al, titled “Toward Understanding Kernicterus: A Challenge to Improve the Management of Jaundiced Newborns” that was published in the February 2006 issue of Pediatrics (2006;117:474–485; doi:10.1542/peds.2005-0395). On page 475, column 2, paragraph 2, the paragraph and equations should read as follows:

The relationship between $B_f$, albumin-bound bilirubin concentration (AB), and serum albumin concentration (A) at clinically relevant TSB and A can be expressed as:

$$B_f = \frac{AB}{(A - AB) \times K}.$$  

Because TSB = AB + $B_f$, and $B_f$ is extremely low relative to TSB, AB $\approx$ TSB, and the equation can be expressed as:

$$B_f \approx \frac{TSB}{(A - TSB) \times K}.$$  

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An erratum has been published regarding this article. Please see the attached page for: http://pediatrics.aappublications.org/content/117/4/1467.2.full.pdf