LETTERS TO THE EDITOR

Pitfalls of meta-analysis

Editor,—The article by Lacy and Ohlsson clearly shows how statistical manipulation of figures can produce differing results from the same basic data.1 The authors with their ‘cau-
tious use of meta-analysis’ find insubstantial evi-
dence of the benefit of IVIG in either pre-
vention or treatment of neonatal sepsis. Using
similar data, Weisman et al found the relative
risk of infection if IVIG prophylaxis was not
used to be large by far (3·2) (mean (SD)), and a
relative risk of death in infected neonates not
with IVIG to be 3·0 (0·7). The authors explain this difference by suggesting use of ‘inappropriate statistical methods’ by Weisman et al.

Lacy and Ohlsson have heavily quoted pub-
lished data in search of ‘good quality’ and ‘homogeneity’. In the field of IVIG nothing thus far has been homogenous. All the pub-
lished data—good or poor quality—have not
toined in entry and outcome criteria but also
in basic definitions of variables such as the
definition of sepsis and mortality from sepsis. Nor have the authors differentiated between mortality and sepsis and that from unrelated
causes or weight groups. Babies that weigh 800
have a higher mortality from causes other
than sepsis than those weighing 2500 g. The
authors have also failed to discriminate
between studies in which a placebo was used
for the control group and studies in which
there was no intervention in the control group.

Another bias in this analysis was the uncrit-
ical acceptance of the infants patient groups
as if they were of comparable severity, gen-
eral condition, and age. The authors ignored
that only Weisman et al have a system of
criteria for looking at the data which allows
supporting the generalization of those results
when analyzing the whole group of patients
only those with identical conditions.

While the authors themselves pointed out,
the studies differed in dose regimen, duration of
treatment, and the IVIG preparation used.
However, they fail to point out two crucially
important differences between preparations:
bioavailability which depends on the method
of preparation and on the consistency in the
sub-class distribution. IgG subclass distribution
in the preparations is of greatest relevance,
taking into account the organs which
cause infection in the neonatal period.

Second, Clapp et al 3 and ourselves have
clearly shown how important it is to attain and
maintain serum IgG above at least 400
mg/dl to be protective—very few studies report
or measure serum IgG, thus making any
comparison extremely difficult, if not
impossible.

It may make statistical sense to reject
studies which are not prospective, blinded,
and controlled, but it makes a nonsense to
compare studies without taking into consider-
atation the very principles on which the whole
concept of IVIG is based. Information such as
bioavailability of the product, serum concen-
trations obtained, and well defined outcome
measure are crucial principles missing from
this meta-analysis. Any conclusions drawn on
this basis are therefore questionable to say the
least. No clinician would use a subtherapeutic
dose of antibiotic, for example, and expect it to
be effective. It is clear, however, that well
designed, large studies with appropriate IVIG are
required.

In our discussion we emphasised that the
lack of benefit for the prophylactic use of
IVIG is based on preparations used to date and
that ‘new preparations of IVIG with other
antibodies or other combinations of antibi-
dies might be effective’.

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1 Lacy JB, Ohlsson A. Administration of intra-
venous immunoglobulins for prophylaxis or
treatment of neonatal sepsis: meta-

2 Weisman LE, Crues DF, Fischer GW. Current
status of intravenous immunoglobulin in pre-
venting or treating neonatal bacterial infections.

3 Fanaroff A, Wright E, Korones S, et al. A
trolled trial of prophylactic intravenous
immunoglobulins to reduce nosocomial infec-
tions in VLBW infants. Ped Res 1992; 32A:
202(A).

4 Morell A. Characterization and safety aspects
of intravenous immunoglobulin preparations.
In: Koch C, ed. Clinical use of intravenous
immunoglobulin. Copenhagen: FADL

5 Clapp DW, Baley JE, Kligeman RM, et al. Use of
intravenously administered immunoglobulin to
prevent nosocomial sepsis in low birth weight
115: 973–8.

Dr Lacy and Ohlsson comment:

Dr Haque compares our meta-analysis with
the review by Weisman et al. In our paper we
used generally accepted methods for a sys-
tematic overview.1 Our statistical synthesis
included a different set of data than those of
Weisman et al. We stand by our original state-
ment that Weisman et al used inappropriate
statistical methods to combine study results—
that is, they appear to have combined individ-
ual study results by using an arithmetic mean
of the relative risks, and thus do not account
for study variance which depends on sample
size and number of outcomes.

To avoid bias, we used explicit criteria for the
inclusion of studies and definitions of out-
comes. Regarding Dr Haque’s criticism of our
use of mortality from all causes other than
death from sepsis, we believe that the out-
come of death from all causes is less subject
to bias than disease specific mortality. Feinstein
has recently written that: ‘An important scient-
ific advance can occur in meta-analysis ... if
the outcomes become confined to deaths,
rather than the inconsistencies and occasional
occasions cited as disease-specific causes of
death’.2

Our use of the random effects model for
pooling of data gave less weight to studies
with large sample size than if we had used the
fixed effects model.

Correction

Please note that figure 2 of the paper by Lacy and Ohlsson (Arch Dis Child 1995; 72:151–5) was incorrectly reproduced and should have looked like this:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker (1)</td>
<td>50/287</td>
</tr>
<tr>
<td>Chirico (10)</td>
<td>2/43</td>
</tr>
<tr>
<td>Christensen (11)</td>
<td>0/10</td>
</tr>
<tr>
<td>Clapp (12)</td>
<td>0/56</td>
</tr>
<tr>
<td>Conway (13)</td>
<td>8/29</td>
</tr>
<tr>
<td>Fanaroff (15)</td>
<td>186/1204</td>
</tr>
<tr>
<td>Magny (18)</td>
<td>24/120</td>
</tr>
<tr>
<td>Malik (25)</td>
<td>3/15</td>
</tr>
<tr>
<td>Spady (26)</td>
<td>17/54</td>
</tr>
<tr>
<td>Weisman (23)</td>
<td>40/372</td>
</tr>
</tbody>
</table>

Overall RR

<table>
<thead>
<tr>
<th>Relative RR (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0001</td>
</tr>
<tr>
<td>0-01</td>
</tr>
<tr>
<td>0-1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>100</td>
</tr>
</tbody>
</table>

Intravenous immunoglobulin (IVIG) prophylaxis: effect on sepsis.

Neonatal meningitis with human parvovirus B19 infection

Editor,—We were interested to read two recent papers by Okumura and Watanabe, on the infections of the central nervous system by human parvovirus B19 (B19) infection.1 2 In these cases, the disease manifest at around school age and not during the neonatal period. Three years ago, we encountered a newborn infant who presented with meningi-
gitis and persistent anaemia, presumably
related to B19 infection.

Case report

A 20 day old girl was admitted with high fever
(39-8°C). She had been born by normal vaginal
delivery, and showed uneventful growth until poor feeding developed on the
17th day of life. On the day of admission, the
infant’s mother had had low grade fever, joint
pains, a rash on all four limbs and headache.
Both the infant and the mother had had close
contact with the infant’s 5 year old brother, who had had erythema infectiosum 17 days previously. Her peripheral leucocyte
count was 10·2×109/l, erythrocyte count
3·91×1012/l, and haemoglobin 127 g/l. A
cerebrospinal fluid (CSF) sample indicated
positive serology (861.1×106 IgM cells/ml,
with 57% lymphocytes and 43% neutrophils),
along with 23×103 red cells/ml, protein 0·54
g/l and glucose 2·7 mmol/l. Serum anti-B19
IgG and IgM tested by enzyme linked
immunosorbent assays (ELISA commercial
assay) were positive in both the infant and the
mother. Routine cultures of CSF, blood, and
throat swabs yielded no pathogenic growth.
Aseptic meningitis were diagnosed, and anti-
biotics (imipenem, cefotaxime, and amikacin)
and gamma globulin were started. Her fever

Figure 2

Summary tables for the whole meta-analysis.

1 Okumura A, Watanabe T. Human parvovirus
B19 and the central nervous system. J Clin Med

2 Feinstein AR. Meta-analysis: statistical alchemy
for the 21st century. J Clin Epidemiol 1995; 48:
71–9.
Pitfalls of meta-analysis.

K. N. Haque

Arch Dis Child Fetal Neonatal Ed 1995 73: F196
doi: 10.1136/fn.73.3.F196

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