Thrombocytopenia and neutropenia are common in the neonatal intensive care unit (NICU). Previous reports estimate that 18 to 35% of patients admitted to a NICU will have one or more platelet counts \( \leq 150,000/\text{uL} \) and 8% will have one or more neutrophil counts \( <1000/\text{uL} \) at some time before discharge. To better understand thrombocytopenia and neutropenia in the ELBW population, we performed an historic cohort analysis of neonates cared for in the four Intermountain Healthcare (IHC) NICUs. From archived electronic records and from paper chart analysis we accessed all platelet counts and all neutrophil counts obtained on these patients. When a platelet count \( \leq 150,000/\text{uL} \) or a neutrophil count \( <1000/\text{uL} \) was identified, we determined the day of life this was first recognized, the duration of the cytopenia, the tests used to discover the underlying causes, the underlying causes that were ascribed, the use of platelet transfusions, IVIG, and rG-CSF, and the mortality rates.

**Methods**

Data were collected as deidentified limited data sets from archived IHC records. The information collected was limited to the complete blood counts and the information displayed in tables and figures of this report. Data were obtained for patients admitted to the NICU at McKay-Dee Hospital, Ogden, UT, LDS Hospital, Salt Lake City, UT, Primary Children’s Medical Center, Salt Lake City, UT, and Utah Valley Regional Medical Center, Provo, UT, USA. For the thrombocytopenia study, patients were included if they had a date of birth from January 1, 2003 through December 31, 2004, and with a birth weight of \( \leq 1000 \)g. For the neutropenia study patients were included if they had a data of birth from July 1, 2002 through June 30, 2005. The IHC Institutional Review Board approved the study.

Descriptive statistics were calculated using Statist (Covarrus, OR). Means and standard deviations were used to express values in groups that were normally distributed, and medians and ranges to express values in groups that were not. Differences in categorical variables were assessed using the \( \chi^2 \) test. A Student t test was used to assess continuous variables. Statistical significance was set as \( p < 0.05 \). All hypotheses were two-tailed.
Results

The thrombocytopenia study consisted of 284 ELBW infants and the neutropenia study consisted of 338. The number of platelet counts obtained per patient ranged from 4 to 411 (median, 24) and the number of neutrophil counts obtained per patient ranged from 1 to 123 (median, 16). The overall incidence of thrombocytopenia was 73% and of neutropenia was 38%.

Thrombocytopenia

The birth weight was lower among the 208 who developed thrombocytopenia (720±150 grams, mean±SD) than among the 76 who did not (808±142 grams, \( p < 0.001 \)). The gestational age at delivery was similar between those who developed thrombocytopenia (26.1±2.2 wks) and those who did not (26.4±2.0 wks, \( p = 0.24 \)). No differences were observed in gender, mode of delivery, five-minute Apgar scores, or race or ethnicity, between those who did vs. did not develop thrombocytopenia.

In 58% of the thrombocytopenic ELBW neonates, the thrombocytopenia was detected in the first three days after birth (Figure 1). Only 20% of those who developed thrombocytopenia had this first recognized after the first week of life. Six cases (3%) were not detected until seven weeks or more.

Thrombocytopenia was more common in the lowest birth weight groups (Figure 2). It was found in 85% of those weighing ≤800g at birth, in 60% of those 801-900 g, and in 53% of those 901-1000g. The duration of thrombocytopenia ranged from less than one day to 50 days. Twenty-one of the 208 (10%) had either very transient thrombocytopenia, or had an erroneously low platelet count, because a repeat count performed within 24 hours was normal without an intervening platelet transfusion.

The lowest recorded platelet count was <20,000/uL in 9% of the thrombocytopenic patients; it was ≤50,000/uL in 38% of the thrombocytopenic patients, and it was ≤100,000/uL in 77%. The remaining 23% had mild thrombocytopenia, with the lowest count between 101,000 and 149,000/uL. The mortality rate did not correlate with the lowest recorded platelet count. Among those with the most severe thrombocytopenia (<20,000/uL) 16.7% died, among those with a lowest count in the range of 20–50,000/uL 16.4% died, among those with a lowest count in the range of 51–100,000/uL 19.7% died, and among those with a lowest count in the range of 101–149,000/uL 14.6% died.

The mortality rates among ELBW neonates who did vs. did not receive platelet transfusions are shown in Table 1. Seventy-five neonates had no thrombocytopenia and no platelet transfusions. Seventy-nine others had thrombocytopenia but no platelet transfusions. One patient (not listed in the table) had a platelet transfusion but was not thrombocytopenic. Thus, 154 ELBW neonates received no platelet transfusions; the mortality rate in this group was 12%. One-hundred-twenty-nine were thrombocytopenic and received one or more platelet transfusions (range, 1 to 51 transfusions/patient). The mortality rate in this group was 23% (\( p < 0.01 \) vs. those who received no platelet transfusions, Table 2). Most of the patients who developed thrombocytopenia and died, did so while their platelet count was still low (Table 1).

The platelet counts that preceded 356 platelet transfusions are shown in Table 2. For patients who had multiple platelet transfusions, information was collected only for their first five platelet transfusions. The minor-
ity of platelet transfusions (8%) were ordered for patients with clinical hemorrhage; most were ordered when no record of clinical hemorrhage was found among the physician or nursing notes. The majority (61%) of these latter prophylactic platelet transfusions were ordered when the platelet count was between 50,000 and 99,000/uL. Twenty-eight percent of the prophylactic transfusions were ordered when the platelet count was in the range of 20,000 to 49,000/uL, and only 2.8% of the platelet transfusions were ordered when the platelet count was <20,000/uL.

Fifty-six percent of the thrombocytopenic neonates had a bacterial culture performed to evaluate the underlying cause of the thrombocytopenia. Forty-nine percent had a DIC screen performed, 10% had CMV cultures performed, 3% had lineograms or other imaging studies in an attempt to detect thrombi, and 2% had chromosomes or other genetic testing as part of the search for an etiology of the thrombocytopenia. Two % had viral cultures or viral titers drawn and <1% had anti-platelet antibody testing performed.

The explanations given for the thrombocytopenia are shown in Table 3. Almost half had no explanation discovered. The most commonly applied explanation for thrombocytopenia was that the patient was SGA or was delivered after PIH. None had a diagnosis made of neonatal alloimmune thrombocytopenia, maternal autoimmune thrombocytopenia, viral infection, or drug-associated thrombocytopenia.

Neutropenia
Demographic features of the ELBW neonates with neutropenia vs. those who did not develop neutropenia, are shown in Table 4. In 53% of the neutropenic neonates, the neutropenia was detected on the first day of life (Figure 3), and in 74% it was detected by day three. Only 22% of those who developed neutropenia did so after the first week of life. Nine cases (7%) were not detected until seven weeks or more.

Neutropenia was slightly more common at the lowest birth weights (Figure 4). It was found in 63% of those weighing <500 g at birth, 44% of those weighing 501 to 600 g, and in 34% of those weighing 801 g
The duration of neutropenia ranged from less than one day to just over seven days (figure 5). Fifty-seven percent (73/128) had transient neutropenia, because a repeat count performed within 24 hours was >1000/uL, but 43% continued to have neutropenia for more than one day. The longest duration observed was 7.5 days.

The lowest neutrophil count recorded, among each of the neutropenic patients, is shown in Figure 6. In just under half (48%) of the cases the lowest recorded count was ≤500/uL. In 21% the lowest recorded count was in the range of 800 to 1000/uL.

The presence of neutropenia did not correlate with mortality rate; neither did the severity (lowest recorded count) of the neutropenia, or its duration (days), correlate with mortality rate. For instance, the mortality rate among those with a lowest recorded count of ≤500/uL (8/45 died 17.8%) was not significantly higher than among those with a lowest recorded count >750/uL (3/27 died 11.1%, p=0.27). However, the highest mortality rate group was those with early-onset bacterial sepsis and neutropenia, where four of six died.

Most of the neutropenic ELBW neonates did not have either IVIG or rG-CSF administered. When IVIG was used, it was ordered in accordance with our published guidelines 100% of the time. When rG-CSF was used, it was

<table>
<thead>
<tr>
<th>Factors identified to explain the thrombocytopenia</th>
<th>Number of patients with thrombocytopenia (n=208) first recognized in the first three days, (n=120) who had this as the likely underlying explanation</th>
<th>Patients with thrombocytopenia first recognized after day three (n=88) who had this as the likely underlying explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained or undiagnosed</td>
<td>101</td>
<td>50</td>
</tr>
<tr>
<td>SGA or PIH</td>
<td>76</td>
<td>55</td>
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<tr>
<td>DIC</td>
<td>40</td>
<td>32</td>
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<tr>
<td>Bacterial infection</td>
<td>36</td>
<td>23</td>
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<tr>
<td>Fungal Infection</td>
<td>12</td>
<td>7</td>
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<tr>
<td>NEC</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Genetic</td>
<td>2*</td>
<td>2</td>
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<tr>
<td>Thrombus</td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>Non-CMV viral infection</td>
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</tbody>
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*One trisomy 18 and one TAR syndrome; ** Right atrial thrombus associated with a peripherally inserted central venous catheter
ordered in accordance with our guidelines 69% of the time.

The likely explanations discovered as underlying antecedents, or causes of the neutropenia, are shown in Table 5. The majority of the cases detected in the first three days after birth were associated with SGA or PIH. The majority of the cases detected after the first three days were associated with NEC or nosocomial infection. Over 1/3 of the cases had no apparent explanation for the neutropenia or were incompletely evaluated. None of the neutropenic patients had studies done to assess the presence of alloimmune or autoimmune neutropenia. None of the patients had neutropenia that persisted beyond 7.5 days.

**Discussion**

Thrombocytopenia and neutropenia are rare in a well baby nursery,8,10 but in a NICU these are relatively common, 18 to 35% reported to have thrombocytopenia and 8% reported to have neutropenia at some time during the NICU stay.11 On the basis of our experience, we speculated that ELBW neonates have a yet higher incidence of thrombocytopenia and or neutropenia. Indeed, in the present study we observed that 73% of ELBW neonates had thrombocytopenia and 38% had neutropenia.

Thrombocytopenia and neutropenia can have origins...
either before or after birth. Due to the retrospective nature of this study, it was not possible to know how many of these had prenatal cytopenia. Furthermore there was no pre-specified list of tests to be performed in order to assess the underlying causes of the cytopenia or measure its duration. However, we speculate that the majority of cases were either of prenatal onset or due to factors arising within the first days after birth. We base this on the finding that most cases were recognized on the first day of life, and only about 20% were identified after the first week.

We observed that about half of the cases of thrombocytopenia or neutropenia had no explanation recognized. In otherwise well-appearing term babies with thrombocytopenia, the diagnosis is likely to be neonatal alloimmune thrombocytopenia or due to maternal autoimmune disease, but we found no documented cases of either of these varieties. Similarly, alloimmune neutropenia is a relatively common condition among neutropenic term neonates, but we observed no cases among these ELBW neonates. We speculate that the lack of immune-mediated cases was the result of inadequate testing in this population.

Platelet transfusions are recommended for neonates who have low platelet counts and clinical bleeding. They are also recommended as prophylaxis against bleeding if the count falls sufficiently low. Precisely how low to permit a platelet count to fall in an ELBW neonate before ordering a platelet transfusion is not known. We found that platelet transfusions were nearly always given for prophylaxis against bleeding rather than to treat active bleeding. We identified no consistent criteria for ordering prophylactic platelet transfusions, but we found that those given platelet transfusions had a mortality rate twice that of those who receive no platelet transfusions. We speculate that this increase in mortality rate is related to the underlying illnesses of those who received platelet transfusions, as opposed to being due to a toxic effect of the transfusions.

We found that 43% of the cases of late-onset neutropenia had no recognized underlying cause. Some of these may have been due to the benign variety of neutropenia sometimes termed, idiopathic neutropenia of prematurity. That variety probably does not constitute a significant host-defense deficiency, because patients generally maintain a bone marrow neutrophil reserve that can be mobilized as needed to contend with bacteria.

IVIG administration has sometimes been advocated for septic, neutropenic, neonates, with the hope of providing opsonic antibody against infecting organisms, but its use has not been well defined. In a recent Cochrane Review of this usage of IVIG, Olson and Lacy concluded that the available data suggest a benefit in reducing mortality. In a consensus development process we suggested that the use of IVIG was reasonable in neonates who had a blood neutrophil count <1000/uL and proven or very likely bacterial sepsis and shock syndrome. In the present study we observed that IVIG was used in accordance with this recommendation. However, it is unclear how much benefit the patients derived from this practice.

rG-CSF has been approved for use among patients with severe chronic neutropenia. Although controversial, rG-CSF has generally not been regarded as useful
In a comprehensive review of the use of rG-CSF, a Cochrane Review concludes that while more study is needed, the available data suggest that it has no significant benefit in reducing mortality. In a consensus development process, we suggested that rG-CSF should not be routinely used to treat neonates who have sepsis and neutropenia, but that it should be reserved for neonates who may indeed have a variety of severe chronic neutropenia, whose neutrophil counts are <500/μL for two days or more, or <1000/μL for five days or more. In the present study we observed that when rG-CSF was used in neutropenic ELBW neonates, it was given in accordance with this recommendation in 69% of the cases. As with IVIG usage among neutropenic ELBW neonates, it is unclear from this study how much benefit these patients derived from rG-CSF administration. In general, we found neutropenia in ELBW neonates to be transient, generally lasting only one day, and rarely more than three. We failed to find an association between neutropenia and mortality, except in the circumstance of proven early-onset bacterial infection where it was associated with a poor outcome. On this basis, we judge that neutropenia among ELBW is generally not a significant host-defense defect, and (except when it accompanies early-onset sepsis) likely needs no specific treatment. For ELBW neonates with early-onset sepsis, neutropenia, and shock syndrome, IVIG administration is based on biologically plausible rationale, but its efficacy requires further study. Since so many of the cases we reviewed were of idiopathic causation, or were incompletely evaluated, we judge that a more consistent approach is needed for evaluating thrombocytopenia and neutropenia in this group of patients. We also judge that additional work is needed to define which cases are truly innocuous and which are likely to benefit from various treatments.

References