Progression of cerebrospinal fluid cell count and differential over a treatment course of shunt infection

Clinical article

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Object. The physiological reaction of CSF white blood cells (WBCs) over the course of treating a shunt infection is undefined. The authors speculated that the CSF WBC count varies with different infecting organisms in peak level and differential percentage of polymorphonuclear (PMN) leukocytes, lymphocytes, monocytes, and eosinophils. The authors hope to identify clinically useful trends in the progression of CSF WBCs by analyzing a large group of patients with successfully treated shunt infections.

Methods. The authors reviewed 105 successfully treated cases of shunt infections at Riley Hospital for Children. The study dates ranged from 2000 to 2004; this represented a period prior to the routine use of antibiotic-impregnated shunt catheters. They analyzed the following organisms: coagulase-negative staphylococci, Staphylococcus aureus, Propionibacterium acnes, Streptococcal species, and gram-negative organisms. The initial CSF sample at diagnosis was analyzed, as were levels over 14 days of treatment. Model fitting was performed to generate curves for the expected progression of the WBC counts and the differential PMN leukocytes, lymphocyte, monocyte, and eosinophil percentages.

Results. Gram-negative organisms resulted in a higher initial (p = 0.03) and peak WBC count with a greater differential of PMN leukocytes compared with other organisms. Propionibacterium acnes infections were associated with a significantly lower WBC count and PMN leukocytes percentage (p = 0.002) than other organisms. The pattern progression of the CSF WBC count and differential percentages was consistent for all infections. There was an initial predominance of PMN leukocytes, followed by a delayed peak of lymphocytes, monocytes, and eosinophils over a 14-day course. All values trended toward zero over the treatment course.

Conclusions. The initial and peak levels of CSF WBCs vary with the infecting organisms. The CSF cell counts showed a predictable pattern during the treatment of shunt infection. These trends may be useful to the physician in clinical decision making, although there is a wide range of variability. (DOI: 10.3171/2011.8.PEDS11236)

Key Words • cerebrospinal fluid • shunt • infection • white blood cell • polymorphonuclear leukocyte • eosinophil

Cerebrospinal fluid shunts remain the mainstay of hydrocephalus treatment. Approximately 5%–8% of newly placed shunts in children become infected. Shunt infections cause tremendous morbidity, possibly death, and large economic costs to the patients. Although there has been extensive research in methods to reduce the incidence of shunt infections, there is little published reference data on the expected values of CSF cells over the treatment course of shunt infection.

We speculated that different infecting pathogens cause differing CSF reactions, reflected in the WBC count and differential percentages of PMN leukocytes, lymphocytes, monocytes, and eosinophils. We evaluated CSF data of 105 successfully treated shunt infections to explore this question. We analyzed the 5 most common infecting organisms at our institution. We chose a 5-year period (2000–2004) prior to the routine use of antibiotic-impregnated shunt hardware, and we analyzed CSF samples obtained at diagnosis and over 14 days of treatment. We then modeled graphic curves over the 14-day treatment period to generate an estimate of the normal inflammatory cell progression.
Methods

We performed a retrospective analysis of all patients younger than 18 years of age with a shunt infection treated at Riley Hospital for Children from 2000 to 2004. These dates were chosen to reflect CSF values prior to the routine use of antibiotic-impregnated catheters. Relevant clinical, radiographic, and operative reports were reviewed. All CSF data points were recorded. Patients with insufficient or unrecorded CSF data values were excluded. The study began after local institutional review board approval.

Our standard treatment for shunt infection is removal of all existing shunt hardware with placement of an EVD. Broad-spectrum antibiotics are instituted and are then tailored to the individual based on the culture and sensitivity. Cerebrospinal fluid is sampled every other day. A new shunt is placed after at least 3 negative samples. The approximate course between shunt removal and replacement is 14 days. Antibiotics are continued for at least 24 hours after replacement of the shunt.

The 3 most common infecting organisms were coagulase-negative Staphylococci, Staphylococcus aureus, and Propionibacterium acnes. We placed all cases involving streptococcal infections (S. agalactiae, viridans, mitis, and oralis) into a single group. For purposes of analysis, we placed Escherichia coli, Pseudomonas aeruginosa, Klebsiella sp., Enterobacter sp., Serratia marcescens, and Neisseria flavaescens into a single group of “gram-negative” organisms. Together, these 5 categories represented 93.1% of all shunt infections treated over the study period (Table 1).

We defined the “initial” data as the first CSF sample in the evaluation for shunt infection, generally collected through a shunt reservoir “tap.” The time was defined as Day 0. We recorded all subsequent values up to Day 14. The “peak” was defined as the highest mean value over the 14-day course. The initial and peak levels were analyzed using ANOVA and Mann-Whitney U-test. The number of patients and the respective infecting organism analyzed are also shown in Table 1.

The progression of the WBCs and differential percentages were analyzed over a 14-day course of treatment. Statistical analysis and model fitting were performed using SPSS for Windows version 18 to plot sensitivity to the false-positive rate and to evaluate the predictive ability of WBC counts and differential percentages in determining the infectious organism. The ROC curve analysis was performed in 101 cases, as insufficient initial data in 4 patients excluded these cases from analysis.

The appropriate function was chosen by determining the nonlinear model that minimized the sum of squares of errors. Note that the curve-model fitting is based on the highest mean value on a particular day. This modeling therefore did not strictly match the numerical “peak” determined by the highest total mean value recorded (Fig. 1, Tables 2 and 3), irrespective of time.

Of 130 treated patients, we excluded patients with insufficient CSF data for analysis, fungal infections, and rare or singular pathogens. We also excluded 12 patients (9.2%) in whom treatment was not successful. These patients either had a secondary infection over the course of treatment or suffered an infection in the immediate posttreatment phase. Overall, 105 (80.8%) of the 130 total patients met the entry criteria for inclusion in the analysis. The number of patients and the respective infecting organism analyzed are also shown in Table 1.

Tests were conducted at a statistical significance (p) of 0.05. Summary data are presented as mean ± SD.

Results

We treated 130 shunt infections over the 5-year study period. The infecting organisms are shown in Table 1. The most common single infecting organisms were coagulase-negative Staphylococcus (36.1%), S. aureus (21.5%), and P. acnes (10.8%). We grouped together streptococcal infections (6.9%) and gram-negative organisms (17.7%). We restricted our analysis to these 5 organisms/groups. One hundred five of the 130 shunt infections met the entry criteria for analysis.

Initial WBC Count and Differential Percentages

The initial mean WBC count and the differential percentage of PMN leukocytes, lymphocytes, monocytes, and eosinophils are shown in Table 2. Statistical analysis of data obtained in 101 of the 105 patients showed that there was a higher percentage of PMN leukocytes in the gram-negative group than all gram positives (p = 0.03, Mann-Whitney U-test).

The ROC analysis revealed a statistically significant area under the curve for PMN leukocyte differential percentage (p = 0.038). A cut-off of PMN leukocyte percentage greater than 62% resulted in the best combination of sensitivity (80%) and specificity (57%) for detecting gram-negative infections.
Propionibacterium acnes was associated with a lower initial WBC count and percentage of PMN leukocytes than all other infections \((p = 0.01)\). An ROC analysis revealed a statistically significant area under the curve for WBC count \((p = 0.026)\). A cut-off of WBCs less than 16 resulted in the best combination of sensitivity \((82\%)\) and specificity \((60\%)\) for detection of P. acnes infection.

No statistically significant differences were noted between the initial WBC count and differential percentages among the other organisms.

**White Blood Cell Count and Differential Progression Over the Treatment Period**

The overall WBC count rose over the treatment period in all organisms. The initial and the peak WBC counts are presented graphically in Fig. 1. The median time to peak WBC count was 3 days \((range 2.5 \text{ days for streptococcal infection to 5.1 days for } P. \text{ acnes})\). The WBC count progression over the treatment course is shown in Fig. 2.

The average peak WBC count was higher in gram-negative organisms than the other organisms \((p = 0.017)\). No statistically significant differences were noted in maximum observed WBC count among the other organisms.

The differential percentages show a consistent progression over all organisms. The highest percentage of PMN leukocytes was reached first, with a range from 2.6 days for streptococcal infections to 5.1 days for P. acnes. Lymphocytes, monocytes, and eosinophils peaked on approximately Days 7–8. The peaks and time to peak are shown in Table 3. Propionibacterium acnes infections exhibited a statistically significantly lower PMN leukocytes peak percentage \((p = 0.002)\) and higher peak eosinophil percentage \((p = 0.02)\).

Figure 3 shows the differential percentages of PMN leukocytes, lymphocytes, monocytes, and eosinophils over the course of treatment. The WBC trends toward zero near the end of the 14 days. There was a high degree of variability in the peak values and differential percentages. This is shown by the relatively high standard deviations across all analyzed data.

**Discussion**

Shunt infections are potentially devastating complications of hydrocephalus treatment. Our institution’s infection rate for initial shunt placement over the study period was 8.3%, closely approximating the rate of 8.1% reported during the multicenter shunt design trial.6 Clinical manifestations of shunt infection include fever, shunt malfunction, malaise, poor feeding, peritoneal signs, a loculated abdominal CSF collection, and wound breakdown.25,32 Previously published risk factors for shunt infection include younger age at insertion, poor skin condition, previous shunt infection, and concurrent infection in a different anatomical location.19,23,30 A shunt infection is diagnosed based on the combination of clinical signs and positive cultures of the CSF or shunt hardware.19,32 While many patients present with classic signs

<table>
<thead>
<tr>
<th>Organism</th>
<th>Initial WBC Count (cells/mm³)</th>
<th>PMN Leukocyte (%)</th>
<th>Lymphocyte (%)</th>
<th>Monocyte (%)</th>
<th>Eosinophil (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>coagulase-negative Staphylococci</td>
<td>387.9 ± 652.8</td>
<td>48.3 ± 31.6</td>
<td>28.7 ± 24.9</td>
<td>19.4 ± 16.1</td>
<td>3.3 ± 4.0</td>
</tr>
<tr>
<td>S. aureus</td>
<td>574.6 ± 1539.0</td>
<td>56.1 ± 26.3</td>
<td>16.6 ± 15.8</td>
<td>22.9 ± 17.3</td>
<td>5.1 ± 6.8</td>
</tr>
<tr>
<td>P. acnes</td>
<td>110.8 ± 163.9</td>
<td>18.0 ± 38.0</td>
<td>37.2 ± 29.0</td>
<td>33.0 ± 32.7</td>
<td>14.4 ± 24.8</td>
</tr>
<tr>
<td>Streptococcal sp.</td>
<td>913.9 ± 1190.9</td>
<td>66.7 ± 41.9</td>
<td>16.7 ± 20.1</td>
<td>16.6 ± 19.6</td>
<td>3.5 ± 4.0</td>
</tr>
<tr>
<td>gram-negative sp.</td>
<td>1618.0 ± 3165.9</td>
<td>69.3 ± 31.6</td>
<td>11.9 ± 12.0</td>
<td>15.6 ± 23.1</td>
<td>6.9 ± 13.2</td>
</tr>
</tbody>
</table>

![Fig. 1. The initial and peak WBC counts of the infecting organisms.](image-url)
of shunt infection, others will have very subtle symptoms. Approximately 10%–40% of patients will not have a fever.5,8,16

A physician may sample the CSF through a reservoir tap or lumbar puncture. A positive CSF culture is considered to be the most specific diagnostic test for shunt infection, although there may be false-negative or false-positive results. The culture results may not be available for a number of days. This is especially true in the more indolent infections (P. acnes), in which the incubation period may be up to 2 weeks.22,31 The clinician may be forced to make clinical decisions based on possibly inconclusive data.

Cerebrospinal fluid leukocytosis in which PMN leukocytes predominate is considered a marker for infection. However, the true “normal” values of WBCs in a child—with or without a shunt—are not precisely defined.10,15,17 Children, especially infants, may have WBCs in the CSF in the absence of infection or neurological pathology.22 Portnoy and Olson21 evaluated CSF samples obtained in 371 children who were proven to not have CNS infection or pathology (seizures). They found up to 3 WBCs in 25% of all children and up to 10 WBCs in 5% of normal neonates. Ahmed et al.1 found a mean of 7.3 WBCs/mm3 in noninfected neonates (range 0–130/mm3).28 Other authors have noted a wide variability of CSF cell counts in children with or without infection.10

There are very few studies examining “normal” CSF cell counts in children with shunt tubing. Lenfestey et al.17 examined the CSF cell levels in 181 neonates with either a VP shunt or CSF reservoir and compared these counts with those in a group of neonates without ventricular catheters. There was no significant difference in baseline WBC counts between the groups. In neonates with a ventricular catheter and infection, there was a mean WBC count of 150 cells/mm3. The authors attempted to identify the appropriate level of WBC sensitive for infection. A level of 100 cells/mm3 had a sensitivity of 100%, a count greater than 30/mm3 had a sensitivity of 75%, and a count greater than 6/mm3 had a sensitivity of 73% in this study.17 Other authors have similarly recommended a level of 100 WBC/mm3 as a predictor of infection, although the number of cases studied is relatively small.16

The CSF leukocyte count in confirmed shunt infections also varies. Conen and associates5 examined 78 shunt infections in patients over 12 years of age. While 80% of patient had a CSF leukocyte count greater than 5 × 106 cells/mm3, a “normal” cell count was present in approximately 20% of patients with infections. Other authors have cited the presence of eosinophils as a marker for infection,18,33 although we previously published data demonstrating that eosinophils may be present without infection.9 Other markers for infection have been studied, including tumor necrosis factor–α, various interleukin concentrations,2 and polymerase chain reaction for amplification of bacterial DNA.4 While these show promise, none is yet widely accepted.

Our data suggest a few generalizations about interpreting the initial CSF sample. Gram-negative organisms tend to have a high WBC count with a predominance of neutrophils. The treating physician may consider choos-

<table>
<thead>
<tr>
<th>Organism</th>
<th>Time to Peak</th>
<th>Peak WBC Count (cells/mm³)</th>
<th>Time to Peak</th>
<th>Peak PMN Leukocytes (%)</th>
<th>Time to Peak</th>
<th>Peak Lymphocytes (%)</th>
<th>Time to Peak</th>
<th>Peak Monocytes (%)</th>
<th>Time to Peak</th>
<th>Peak Eosinophils (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>coagulase-negative Staphylococci</td>
<td>3.3</td>
<td>778.3 ± 191.96</td>
<td>3.3</td>
<td>52.3 ± 26.5</td>
<td>7.0</td>
<td>65.5 ± 26.5</td>
<td>7.0</td>
<td>38.5 ± 26.5</td>
<td>6.8</td>
<td>22.1 ± 26.5</td>
</tr>
<tr>
<td>S. aureus</td>
<td>4.4</td>
<td>820.8 ± 1527.4</td>
<td>4.1</td>
<td>65.8 ± 22.5</td>
<td>9.1</td>
<td>43.4 ± 22.5</td>
<td>7.3</td>
<td>32.2 ± 17.1</td>
<td>6.8</td>
<td>5.5 ± 17.1</td>
</tr>
<tr>
<td>P. acnes</td>
<td>5.1</td>
<td>446.9 ± 612.0</td>
<td>5.1</td>
<td>28.5 ± 31.7</td>
<td>7.3</td>
<td>47.4 ± 32.7</td>
<td>8.5</td>
<td>31.8 ± 21.1</td>
<td>7.7</td>
<td>10.9 ± 21.1</td>
</tr>
<tr>
<td>Streptococcal sp.</td>
<td>2.5</td>
<td>1614.9 ± 2398.99</td>
<td>2.5</td>
<td>66.1 ± 28.2</td>
<td>6.8</td>
<td>66.1 ± 28.8</td>
<td>6.8</td>
<td>38.7 ± 26.4</td>
<td>6.1</td>
<td>35.1 ± 26.4</td>
</tr>
<tr>
<td>gram-negative sp.</td>
<td>3.8</td>
<td>4203.1 ± 3815.95</td>
<td>3.7</td>
<td>71.1 ± 33.2</td>
<td>6.8</td>
<td>71.1 ± 33.2</td>
<td>6.8</td>
<td>20.8 ± 25.8</td>
<td>7.7</td>
<td>31.9 ± 25.8</td>
</tr>
</tbody>
</table>

* The time to peak is measured from the initial CSF sample recorded (Day 0).
ing an antibiotic regimen that covers gram-negative organisms in a patient with clinical signs of shunt infection and a CSF sample with a high WBC count with greater than 62% PMN leukocytes.

Conversely, we observed that cases of *P. acnes* infections had a statistically significantly lower percentage of PMN leukocytes (*p* = 0.002), with a higher peak percentage of eosinophils (*p* = 0.02). This clinical scenario may be more challenging than one in which the patient has an extremely elevated WBC count. Confounding matters, *P. acnes* may be present as a contaminant in thioglycolate broth. Anaerobic cultures with a prolonged incubation may be required for growth. The clinician should suspect *P. acnes* in the patient with clinical signs of shunt infection, but with a CSF WBC count of less than 16 with the presence of eosinophils.

All organisms showed a predictable pattern of cell count progression. With the exception of *P. acnes*, the

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**Fig. 2.** Progression of CSF WBC count modeled over a 14-day treatment course. The y axis is graphed in logarithmic scale.

**Fig. 3.** Progression of CSF PMN leukocytes count. The y axis represents a total count rather than percentage (A), CSF monocyte count (B), CSF lymphocyte count (C), and CSF eosinophils (D) over a 14-day treatment course.
initial WBCs were predominately PMN leukocytes. The peak WBC count generally came a few days after presentation. Following the initial influx of PMN leukocytes, all organisms showed delayed peaks of lymphocytes, monocytes, and eosinophils. All organisms showed progression toward zero over the 14-day treatment period.

The study group consisted of 105 patients with successfully treated shunt infections. Consistent with previously published literature, gram-positive organisms represented the most common infecting pathogen. \(^6\)\(^,\)\(^11\)\(^,\)\(^14\)\(^,\)\(^19\)\(^,\)\(^27\)\(^,\)\(^29\)\(^,\)\(^32\) The study period (2000–2004) was chosen to represent a time prior to the routine use of antibiotic-impregnated shunt catheters. We have noted a decrease in the incidence of shunt infection with routine use of these catheters, similar to the results of other authors. \(^3\)\(^,\)\(^7\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^20\)\(^,\)\(^24\)\(^,\)\(^27\)

Anecdotally, we have also noted a change in the epidemiology of shunt infections. The expected distribution of infectious organisms may be changing, with a higher relative percentage of gram-negative infections. While others have not seen an increase in “late” shunt infections, \(^26\) we believe this should be studied more thoroughly. We are currently in the process of collecting data during a 5-year period in which antibiotic catheters were routinely used. We hope to compare these data to those reported in this article. The standard ideas of the rate, epidemiology, and physiological reaction of shunt infections may need to be revisited.

**Study Limitations**

Children with hydrocephalus often represent complicated cases with multiple comorbidities. In the present analysis, we did not examine variables such as age or cause of hydrocephalus. Our hope was that these factors would average with a large study population. However, we do know from the literature that neonatal patients may have multiple comorbidities that increase the risk of shunt infection, may normally have WBCs in the CSF, and often undergo shunt treatment for hydrocephalus resulting from intraventricular hemorrhage. It is possible that neonatal patient reaction to infection differs from that of older patients in whom the cause of hydrocephalus differs.

Another finding, both in this paper and previous publications, is the wide variability in the physiological reaction to infection. In our article, this is shown by the large standard deviations across all mean values. Therefore, the comparisons of initial/peak data and the modeling curves should be viewed as suggestive trends rather than absolutes.

**Conclusions**

The physiological reaction to shunt infection follows a predictable pattern of an initial predominance of PMN leukocytes, followed by a later peak of lymphocytes, monocytes, and eosinophils. All values trend toward zero with successful treatment of shunt infection. The pattern and levels of WBCs vary with organisms. Gram-negative organisms trend toward a higher WBC count with an early peak and higher percentage of PMN leukocytes. *Propionibacterium acnes* has a lower PMN leukocytes percentage, lower overall WBC count, and a higher percentage of eosinophils. These data may serve as a baseline to interpret CSF samples, both at the initial sampling and through the course of treatment. They may also serve as a baseline against which to compare the effects of antibiotic-impregnated catheters.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fulkerson. Acquisition of data: Fulkerson, Edwards. Analysis and interpretation of data: Fulkerson, Sivaganesan, Hill, Edwards, Shoja, Jea. Drafting the article: Fulkerson, Sivaganesan, Hill, Edwards, Boaz, Jea. Critically revising the article: Fulkerson, Sivaganesan, Hill, Boaz, Jea. Reviewed submitted version of manuscript: Fulkerson. Approved the final version of the manuscript on behalf of all authors: Fulkerson. Statistical analysis: Sivaganesan, Shoja. Study supervision: Fulkerson.

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