Correspondence

Table 1. Characteristics of 61 patients with tropical spastic paraparesis/human T lymphotropic virus type 1 (HTLV-1)–associated myelopathy (TSP/HAM), by sex.

Variables	Female patients (n = 42)	Male patients (n = 19)	All patients (n = 61)
Age, mean years ± SD (range)	49 ± 11 (23–74)	41 ± 12 (24–72)	49 ± 12 (23–74)
Time from symptom onset to diagnosis of TSP/HAM, years	9 ± 1	9 ± 1	9 ± 1
Age of TSP/HAM diagnosis, years	49 ± 12	50 ± 15	49 ± 13
Age of onset of TSP/HAM symptoms, years	40 ± 11	41 ± 18	41 ± 13
HTLV-1 load, copies/10^4 PBMCs	889 ± 1668	1117 ± 1580	950 ± 1595

NOTE. Data are mean value ± SD, unless otherwise indicated. Only 3 men received a diagnosis of TSP/HAM when they were >60 years of age.

Low Risk of Tropical Spastic Paraparesis/Human T Lymphotropic Virus Type 1–Associated Myelopathy Development among Persons Aged >50 Years

To the Editor—Tropical spastic paraparesis/human T lymphotropic virus type 1 (HTLV-1)–associated myelopathy (TSP/HAM) is an immune-mediated disease [1] characterized by chronic, slowly progressive, spastic paraparesis with bladder disturbances, absent or mild sensory loss, and lower back pain in the absence of spinal cord compression, as well as by seropositivity for HTLV-1 antibodies [2]. Although the usual presentation is characterized by a slow progression, 21.5% of the patients may experience a rapid progression, with severe disability developing 2 years after the onset of symptoms [3].

The estimated incidence of TSP/HAM ranges from 0.25% to 1% after 30–40 years of incubation [4]. The mean age of onset of disease is 40 years, and the disease occurs predominantly in women [5]. Several factors have been ascribed as effecting clinical outcome, including high HTLV-1 load [6], genetic background [7], route of transmission (i.e., breastfeeding or transfusion), and high antibody titers [8]. Because of the range of clinical evolution of progression, we decided to assess the time of onset of signs and/or symptoms of TSP/HAM in our HTLV Service in Sao Paulo, Brazil.

Over the past 10 years, our research group has observed 360 HTLV-1–infected patients, 61 of whom have received a diagnosis of TSP/HAM. During the follow-up period, 2 additional patients (among 299 healthy asymptomatic carriers) developed TSP/HAM (data not shown), with diagnosis based on revised Kagoshima criteria [9]. Both patients were <30 years of age, and their parents had also received diagnoses of TSP/HAM. Overall, the mean age of TSP/HAM development was 47 years, and the mean age at onset of symptoms was 40 years. None of the asymptomatic carriers aged >50 years developed symptoms during the follow-up period. Although 3 men received a diagnosis when they were >60 years of age, initial symptoms primarily occurred in individuals aged <40 years (table 1). HTLV-1 DNA loads were similar, regardless of sex and age.

In contrast to adult T cell leukemia, the incidence of TSP/HAM decreases with age. Thus, the progression of TSP/HAM is similar to that of multiple sclerosis; for both conditions, few cases have been reported in persons aged >60 years [10]. A possible explanation for this is that, because TSP/HAM is an immune-mediated illness, lack of $CD8^+$ cell hyperactivity in older patients decreases the risk of clinical development [11]. This observation may have implications for counseling and medical practices in areas where HTLV-1 infection is endemic.

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Pneumococcal Necrotizing Pneumonia and Pleural Fluid Lactate Dehydrogenase Level

To the Editor—I read with interest the recent article by Bender et al. [1] about pneumococcal necrotizing pneumonia (NP) in children. The results of the study confirm the severity of this entity in children (as reported elsewhere [2–4]), and the study enhances the previous findings with more detailed serotype analysis. Similar to the findings of Bender et al. [1], we have recently seen at our institution severe presentations and bad outcomes of pneumococcal NP associated with serotype 3 and other serotypes [5, 6]. Of concern to us, very high initial lactate dehydrogenase (LDH) levels were seen in pleural fluid specimens obtained from children who received an initial diagnosis of pneumococcal empyema and who subsequently developed severe NP and required extensive decortications, segmentectomies, or lobectomies. In retrospect, some of these children eventually would have benefited from earlier surgical interventions.

Although children with complicated pneumococcal pneumonia who require decortication drainage may have higher levels of LDH in pleural fluid [7], it is uncertain whether patients with pneumococcal NP exhibit significantly higher LDH levels in pleural fluid, compared with patients with NP due to *Staphylococcus aureus* or other organisms. In the 2 largest series of NP in children, an in-depth analysis of this issue was not performed [8, 9]. Similarly, studies comparing pleural fluid LDH levels in children with complicated pneumococcal pneumonia caused by non-pneumococcal conjugate vaccine–7 serotypes versus pneumococcal conjugate vaccine–7 serotypes have not been performed.

LDH, a useful parameter in pleural fluid analysis for patients with complicated pneumonia (among others), reflects cellular injury and can be released by cells undergoing either primary or secondary necrosis. Recent research findings in mice have revealed that, during severe pulmonary inflammation (i.e., bacterial pneumonia), apoptotic neutrophils undergoing secondary necrosis are the primary source of LDH in bronchoalveolar lavage fluid [10]. The clinical relevance of these findings is unknown for children with complicated pneumonia; however, it is likely that these changes also occur in the lungs of individuals with NP, which may partially explain the elevated LDH levels seen in these individuals. These high or abnormally high values should alert clinicians about the possibility of ongoing necrosis or liquefaction of the pulmonary parenchyma, and clinicians must give special attention to this issue in the present era, in which NP is more commonly reported.

The study by Bender et al. [1] is admirable, and I understand that the objectives that they intended at the beginning were different from the issues that I discuss here. However, considering that their study involved children with necrotizing pneumonia, mention of other aspects of this entity is important and would benefit their study. No mention was made about pleural fluid LDH levels or about findings of examination of lung biopsy specimens from those who underwent surgical procedures and the respective intraoperative findings. Could the authors provide LDH findings in this cohort (i.e., ranges and mean values)? Were there any serotypes associated with higher levels of LDH?

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Reply to Ulloa-Gutierrez

To the Editor—We thank Dr. Ulloa-Gutierrez [1] for his interest in our recent article about the association of *Streptococcus pneumoniae* serotypes with necrotizing pneumonia in children in Utah [2]. Ulloa-Gutierrez [1] addressed parameters other than *S. pneumoniae* serotype that may be predictors of severity. Specifically, an elevated lactate dehydrogenase (LDH) level appears to be associated with severe necrotizing pneumonia caused by serotype 3 in the Hospital Nacional de Niños de Costa Rica (San José) [1]. An elevated LDH level likely represents cellular damage to lung parenchyma, and it is reasonable to hypothesize that the degree of elevation correlates with the extent of necrosis. If *S. pneumoniae* serotype 3 causes more extensive necrosis, it stands to reason that LDH levels will be more elevated in patients with pneumonia caused by serotype 3.

At the suggestion of Ulloa-Gutierrez [1], we retrospectively evaluated the pleural fluid LDH levels in the 14 patients with serotype 3 pneumonia in our study. Five of the 14 patients had pleural fluid LDH levels measured. The median LDH level was 49,460 U/L (range, 39,700–118,041 U/L). These values represent a 40–120-fold increase over the upper limit of normal for serum LDH level in our laboratory (975 U/L). These findings appear to be consistent with those of Ulloa-Gutierrez [1]. However, care should be taken when comparing pleural fluid indices from retrospective studies because of the variability in time to presentation and other clinical and laboratory factors.

Complicated pneumonia in children is a growing problem worldwide. We agree with Ulloa-Gutierrez [1] that pleural fluid indices might prove to be a useful adjunct in predicting outcomes and directing management. In a separate study, we demonstrated that among children with empyema, those with pleural fluid indices including higher WBC counts, lower glucose values, and the presence of bacteria on Gram stain or culture were more likely to require surgical intervention than were those without these findings [3]. The degree of LDH elevation, however, was not associated with the need for surgical intervention.

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Natural Products and Wound Management: A Never-Ending Story

To the Editor—Kwakman et al. [1] evaluated the efficacy of Revamil medical-grade honey as a topical antimicrobial agent for prevention or treatment of infection, including those caused by multidrug-resistant bacteria, and they proposed this natural product for the treatment of wound infections. Their article raises some questions about the use of natural products in modern medicine and about what can be learned from the medical practices of ancient centuries [1].

In some ways, the history of medicine is strictly bound to the care of wounds, especially those injuries caused in battles. In Mesopotamia (2100 BC), after cleaning a wound with beer, a bandage with wine and turpentine was applied. In Ancient Egypt, a natural product, such as honey, became common in wound management: after irrigating a wound with wine, physicians would then cover the wound with fat and honey. In Greece, during the time of Homer, wounds were covered and treated with herbs, whereas infected wounds were healed by dropping scrapings from bronze spears into them.

Four hundred years later, Hippocrates taught that wounds should be washed with wine, bandaged, and then saturated with more wine. Galen, of ancient Rome, cleaned wounds with vinegar but nevertheless believed that suppuration *("pus bonum et laudabile")* was necessary for healing. This belief prevailed for many centuries.

When gunpowder was first used in battle, boiling oil was used as wound treatment, with the aim "to inactivate" the gunpowder effect within gunshot wounds.

This practice was abandoned when, in 1542, Ambroise Paré performed one of the first cohort studies to demonstrate that egg yolk and turpentine were better than boiling oil for treatment of gunshot wounds.

There are limited data on natural products, such as yogurt (which seems to help in controlling wound odor [2]), tea tree oil, and potato peelings; however, there is a great interest in the use of honey for wound healing [3]. Indeed, honey kills staphylococci [4], including the fearsome community-acquired methicillin-resistant *Staphylococcus aureus* [5], within a few hours; it has anti-inflammatory activity [6]; and its hypertonicity provides antiseptic activity. However, clinical data on the effect of honey on wound management are controversial [7, 8], often because of the low quality of some studies [9] and perhaps because of different antimicrobial activities of different honey types [10].

Although science and technology march ever forward, we must not fail to exploit the potential of natural products, because they may represent—as in ancient times—a hope for modern medicine.

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Antiviral Activity of Cidofovir and Ribavirin against the New Human Adenovirus Subtype 14a That Is Associated with Severe Pneumonia

To the Editor—Louie et al. [1] have described 3 cases of severe pneumonia caused by a new pneumotropic human adenovirus subtype 14a (HAdV-B14a). Moreover, several outbreaks of HAdV-B14a infection with a high mortality have been described in the United States, suggesting emergence of a highly pathogenic virus [2]. The emergence of HAdV-B14a as a respiratory pathogen has also been observed at US military training centers [3].

An experimental antiviral therapy with cidofovir for a single case of HAdV-B14a pneumonia was reported by Louie et al. [1], although it achieved limited clinical success. HAdV-B14a is a member of species B (subspecies B2) human adenoviruses. In vitro susceptibility of human adenoviruses to antiviral drugs is species dependent. Human adenoviruses of species C have been shown to be susceptible in vitro to both ribavirin and cidofovir, whereas the susceptibility of human adenoviruses of other species to ribavirin has been shown to be significantly lower [4, 5]. Nevertheless, testing the in vitro susceptibility of HAdV-B14a to ribavirin seems to be reasonable, because high concentrations of ribavirin (>1000 μM) can be achieved in respiratory secretions with use of high-dose aerosol therapy, which has been developed for treatment of respiratory syncytial virus infection [6].

Therefore, we tested the antiviral activity of cidofovir and ribavirin against HAdV-B14a (Portland isolate, generously provided by D. Erdmann, Centers for Disease Control and Prevention). A rapid quantitative PCR-based assay for testing antiviral agents against human adenoviruses on a lung cancer cell line (A549) was used as described elsewhere [5]. Human adenovirus type 5 of species C (HAdV-C5) served as a positive control. In vitro susceptibility of HAdV-B14a to cidofovir was high and in the same range as that of in vitro susceptibility of HAdV-C5. Peak plasma levels reported after intravenous

Table 1. Antiviral activity of ribavirin and cidofovir against human adenovirus type 5 of species C (HAdV-C5) and human adenovirus subtype 14a (HAdV-B14a) in a lung cancer cell line (A549 cells).

	Ribavirin		Cidofovir	
Species	IC_{50}	IC_{90}	IC_{50}	IC_{90}
HAdV-B14a	2.6 (1.9–3.7)	734.3 (388.0–1557.4)	0.8 (0.7–0.9)	16.0 (12.1–21.9)
HAdV-C5	1.7 (1.1–2.8)	29.0 (15.1–64.4)	0.4 (0.3–0.5)	19.4 (12.1–33.9)

NOTE. Data are expressed as mean μM (95% CI). IC_{50}, 50% inhibitory concentration; IC_{90}, 90% inhibitory concentration.

application of 5 mg of cidofovir per kilogram of body weight were ~5-fold higher than an inhibitory concentration of 90% (IC_{90}) against HAdV-B14a (table 1) [7]. Thus, cidofovir holds promise to be active against HAdV-B14a replication in vivo. In the case of ribavirin, the low 50% inhibitory concentration (IC_{50}) value suggested an in vitro susceptibility of HAdV-B14a that is similar to that of HAdV-C5 (table 1). However, a 90% inhibition of HAdV-B14a replication was not achieved with noncytotoxic concentrations (table 1; 50% cytotoxic concentration of ribavirin, 802 μM). For comparison, 90% inhibitions of HAdV-C5 and HAdV-B11, which is closely related to HAdV-B14a, were achieved with noncytotoxic ribavirin concentrations of 29 μM and 38 μM, respectively [5]. Therefore, the interpretation of HAdV-B14a in vitro susceptibility data requires caution, in spite of very high concentrations (>1000 μM ribavirin) achieved in respiratory secretions by high-dose aerosol therapy.

In conclusion, intravenous application of cidofovir should reach a plasma concentration well above in vitro IC_{50} and IC_{90} values for HAdV-14a. Although lung concentrations may be lower and early initiation of therapy may be crucial, cidofovir holds promise as an antiviral agent for the treatment of severe lower respiratory tract infections caused by HAdV-B14a. By contrast, high IC_{90} values of ribavirin in the range of cytotoxic concentrations may lead to clinical failure, although high alveolar concentrations can be achieved using aerosolized ribavirin.

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Glycerol and Dexamethasone in Bacterial Meningitis in Low-Income Countries: Response to the Editorial Commentary by Sáez-Llorens and McCracken Jr.

To the Editor—Some of the comments and observations by Sáez-Llorens and McCracken Jr. [1] regarding the study by Peltola et al. [2], in which the role of glycerol and dexamethasone in acute bacterial meningitis has been evaluated, are provocative and need discussion, particularly after the response by Peltola and Roine [3].

Sáez-Llorens and McCracken Jr. [1] raised ethical concerns about the use of placebo and contend that, because of the use of placebo, many children with bacterial meningitis were subjected to an unnecessary risk of sequelae. Given the current evidence, we do not believe that this is true. A recent meta-analysis supports the use of adjunctive corticosteroids for children in high-income countries only [4]. For children in low-income countries, corticosteroids had no beneficial effect on mortality (risk ratio [RR], 0.96; 95% CI, 0.78–1.18), severe hearing loss (RR, 1.04; 95% CI, 0.66–1.63), and short-term neurological sequelae (RR, 1.08; 95% CI, 0.82–1.44). For children in low-income countries, the use of corticosteroids was not associated with either beneficial or harmful effects [4].

In low-income countries, many of the patients have underlying malnutrition and frequent infections, and they often do not approach a health care facility until late in the course of an illness. These factors are likely to affect cortisol production and levels of cortisol in plasma and may affect the outcome of a critical illness. Malnourished children with or without acute infection have hypercortisolemia and impaired clearance of exogenous cortisol [5–7]. However, the expected metabolic effects of increased cortisol and other glucocorticoid agonists are blunted in these children, because of resistance to glucocorticoids secondary to downregulation of glucocorticoid receptor protein, expression of an inactive form of the glucocorticoid receptor protein, or repression of phosphorylation of the glucocorticoid receptor/hormone complex [7, 8].

In a study from our center, serum cortisol levels in patients who had acute bacterial meningitis were very high. Only 2 of 30 patients had serum cortisol levels in the normal range (20 ng/mL in 1 patient and 50 ng/mL in the other) [9]. The levels correlated with the severity of illness as assessed using the Glasgow Coma Scale. We contend that the therapeutic use of exogenous steroids in patients in low-income countries who already have very high endogenous corticosteroid secretion may not be effective, and this may explain the lack of benefit from dexamethasone

treatment that has been reported in studies from developing countries [10]. Until such time that new data or meta-analyses are available to define the reasons for different outcomes in high-income versus low-income countries and to identify those children in low-income countries who could benefit form corticosteroids, the role of adjunctive corticosteroids for the treatment of acute bacterial meningitis in low-income countries remains uncertain.

We have also conducted a study [11] that used a protocol similar to that used by Peltola et al. [2]. Our study was approved by the ethics committee of our institution without any concerns. We did not find any difference in outcomes among patients treated with glycerol, dexamethasone, or placebo. However, we found that children who received glycerol had a mean 3% elevation of serum osmolality during the first 6 h after treatment, and this elevation was sustained for 24 h. This could have contributed to lowered intracranial pressure and improved cerebral perfusion and, therefore, reduction of sequelae associated with bacterial meningitis [12].

A prerequisite for a "favorable" effect of dexamethasone treatment in patients who have bacterial meningitis is that it be administered before the first dose of antibiotic. In reality, a large number of patients in developing countries report to the hospital late in the course of the disease and may have received $\geq$1 antibiotics before reporting to a hospital [13]. Therefore, not using dexamethasone as an adjunct is not unreasonable.

In the absence of clear proof of the benefit of dexamethasone therapy for the treatment of bacterial meningitis, the deleterious effect of a high cortisol level on neurological outcome cannot be discounted. Glucocorticoids produce a generalized metabolic vulnerability in neurons that possess a high concentration of corticosterone receptors [14]. The use of dexamethasone in such a scenario could perhaps raise ethical concerns.

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Reply to Singhi et al.

To the Editor—In the concluding paragraph of our commentary regarding the study by Peltola et al. [1], we stated "that the most effective strategy of managing bacterial meningitis and its associated sequelae is prevention by implementing large-scale immunization strategies against the common meningeal pathogens.…We urgently need a dedicated collaborative effort between vaccine manufacturers, philanthropic foundations, global health organizations, and national governments to make these vaccines available for those who need them most: the infants and children living in less advantageous areas of the world [2, pp. 1288–9]."

We do not believe that additional discussion of whether dexamethasone or glycerol is more effective as adjunctive therapy for bacterial meningitis in infants and children from very low income nations is a useful exercise. These agents have a relatively small impact in those who are most severely affected, compared with the impact of prevention of disease by vaccination.

Singhi and Singhi [3] took issue with our concern regarding the use of placebo in children with bacterial meningitis in the study by Peltola et al. [1]. They misread our commentary. We questioned the use

of placebo for the treatment of meningitis in countries where disease due to *Haemophilus influenzae* type b (Hib) predominates. This was the case in the Latin American countries included in the study by Peltola et al. [1], in which 221 (45.7%) of 484 patients had meningitis caused by Hib. Stratifying the outcomes for patients with disease due to Hib into dexamethasone versus non-dexamethasone recipients from the Peltola et al. [1] study illustrates our point. Severe neurologic sequelae were observed in 4 (4.5%) of 88 and 9 (9.5%) of 95 patients who received dexamethasone or did not receive dexamethasone (difference is not statistically significant), whereas profound hearing loss was observed in 5 (5.5%) of 91 and 16 (17.8%) of 90 patients ($P = .01$), respectively. This was likely a concern for 2 institutions in Buenos Aires that decided not to administer the placebo-placebo regimen to their patients who were enrolled in that study [1].

In a previous study, Singhi and Bansal [4] showed that serum cortisol concentrations in children with bacterial meningitis were high, especially in those with very severe disease, as assessed using the Glasgow Coma Scale. They contend that the use of exogenous corticosteroids in these patients would likely be ineffective, but they provide no direct evidence to support this contention. Their study [4] used a protocol design similar to that of Peltola et al. [1], and it was too underpowered (56 patients divided among 4 therapeutic arms) to make any conclusions. However, in the analysis of the data from the Latin American study, Peltola and colleagues demonstrated that dexamethasone or glycerol alone or the combination of the 2 agents prevented hearing impairment (measured at 80, 60, or 40 dB), regardless of the causative organism or timing of adjunctive therapy (H. Peltola, personal communication). The only factor that independently predicted hearing loss was the severity of illness at the time of diagnosis; each lower score in the Glasgow Coma Scale increased the risk of impairment by 15%–20%.

As emphasized elsewhere [5], the only effect of dexamethasone in the treatment of meningitis is to modulate the secondary meningeal inflammatory response that follows the initial dose of a parenterally administered, bactericidal antibiotic, and the principal clinical benefit in children is the reduction of hearing loss. Corticosteroids do not reverse CNS damage that has already developed as a result of inflammation, cerebral edema, increased intracranial pressure, and vascular thrombosis. This certainly applied to the children with severe meningitis who were treated in Malawi [6], where undernutrition, concomitant HIV infection, young age, antimicrobials with poor activity, and delayed presentation resulted in very high case-fatality and long-term morbidity rates for disease due to Hib and *Streptococcus pneumoniae,* regardless of whether dexamethasone was administered.

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