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Enteroviral Meningitis

Cost of Illness and Considerations for the Economic Evaluation of Potential Therapies

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Abstract

With limited financial resources available, it is now becoming more acceptable to evaluate medical innovations in terms of incremental economic value. The purpose of this paper is to provide an overview of enteroviral meningitis and to summarise the economic literature to identify relevant costs and outcomes.

Enteroviral meningitis is the most common cause of aseptic meningitis, and occurs in 4.5 to 30 per 100 000 population annually with a duration of illness lasting between 1 and 2 weeks after onset of initial symptoms. The major resource categories that contribute to the overall direct costs of management of enteroviral meningitis include physician visits, hospital admissions, emergency room visits, medications, procedures such as lumbar puncture and computed tomography scans, re-hospitalisations and follow-up physician visits. Indirect costs are incurred in terms of school or work days missed or restrictions in daily activities. The total direct costs of an episode of enteroviral meningitis range from $US450 for outpatients to $US5093 for inpatient management (1996 values). The total indirect costs of an episode of enteroviral meningitis are estimated to be equivalent to 5 to 7 activity-restricted days.

Interventions that improve early diagnosis or decrease the duration and need for hospitalisation will significantly affect the cost of managing enteroviral meningitis. Additional prospective studies are needed to study the impact of interventions on the burden of enteroviral meningitis.

As part of routine clinical practice, outcomes are assessed as an indicator of success. More recently, with the rising expenditures of medical care, attention is being paid to the costs of providing such care. With limited financial resources available, it is now becoming more acceptable to evaluate medical innovations in terms of incremental economic value.

It has long been argued that cost-of-illness studies should be used routinely as a mechanism to identify research agenda and allocate funding for medical innovation in areas that require greatest attention. However, in doing so, diseases causing significant morbidity, but minimal mortality, that occur in small groups of people may often be neglected. Enteroviral meningitis is one such example.

The purpose of this paper is to provide an overview of enteroviral meningitis and to summarise the economic literature to identify relevant costs and outcomes.

1. Enteroviral Meningitis

1.1 Clinical Presentation and Diagnosis

Enteroviral meningitis, the most common cause of aseptic meningitis, is described as an 'inflammatory disorder involving the leptomeninges without evidence of a bacterial or fungal aetiology' and usually with no evidence of parenchymal involvement.[1] The syndrome often presents with fever, headache and meningeal irritation. In older children, adolescents and adults the clinical findings may include malaise, myalgia, photophobia, nausea and emesis. Mild lethargy and drowsiness may also be present. Signs of meningeal irritation (nuchal rigidity, Kernig's and Brudzinski's signs) are generally mild. In infants and younger children, the clinical presentation may be subtle and consist only of fever, irritability, lethargy and poor feeding.

In diagnosing enteroviral meningitis, an examination of the CSF typically reveals a mild to moderate pleocytosis that initially may exhibit a polymorphonuclear cell predominance. In later stages of the infection, a shift toward a mononuclear cell predominance is found. The CSF protein level is, generally, mildly to moderately increased, and the CSF glucose level is almost always normal.

In addition to these routine studies, CSF and blood cultures should be obtained to rule out bacterial (including tuberculosis) and fungal infections and expedite identification of viral involvement.[2,3] Although clinical presentation alone may be used to establish the diagnosis of herpes simplex virus (HSV), polymerase chain reaction (PCR) detection of HSV and enterovirus, where available, may be performed for rapid diagnosis that permits earlier therapeutic intervention if necessary.

1.2 Management

The primary form of management of enteroviral meningitis should be prevention via childhood immunisation against polio and mumps virus. This section addresses current management of patients with suspected CNS infection.

In the majority of patients, infants and children in particular, in whom CNS infection is suspected, hospitalisation is required while awaiting diagnostic test results and initiating empirical antimicrobials. In addition to supportive care such as analgesics/antipyretics for control of pain and fever, and intravenous fluids for dehydration, many physicians choose to initiate empirical antimicrobial therapy in the event that the patient has a bacterial infection. Typically, ceftriaxone or cefotaxime is used while awaiting results of bacterial cultures of the CSF, blood and urine.[4] A computed tomography (CT) scan or magnetic resonance image (MRI) of the brain may be ordered to rule out abscess or lesion. Additionally, in suspected cases of HSV CNS infection, intravenous aciclovir (acyclovir) is administered. Given the significant morbidity and mortality associated with HSV encephalitis, if HSV is a strong clinical possibility, aciclovir should be continued regardless of a negative viral culture.[1] Additionally, diagnostic modalities such as MRI or PCR should be pursued to exclude the diagnosis.

If the patient is clinically well and the results of the bacterial culture are negative at 48 to 72 hours, empirical antibacterial therapy is discontinued, and the patient is discharged with a scheduled follow-up office visit. Full recovery of the patient takes approximately 1 to 2 weeks from the initial onset of symptoms.

1.3 Incidence and Epidemiology of Enteroviral CNS Infections

The overall incidence of aseptic meningitis based on hospitalised cases is in the order of 4.5 to 30 per 100 000 population per annum.[5,6] However, model-based studies suggest that the incidence, including nonhospitalised cases, could be as high as 2 million per year in the US.[7] Typically, aseptic meningitis

1 In the US, the incidence of neonatal HSV has been reported to range from 1 per 3000 to 20 000 live births. HSV1 accounts for approximately 25% of cases whereas HSV2 comprises the remaining 75%. In adults, HSV2 meningitis associated with primary genital infection does occur and is generally not treated. Multiple studies have documented the importance of early and aggressive (i.e. parenteral therapy) for encephalitis secondary to HSV. Typically, treatment of HSV encephalitis and the majority of cases of meningitis in children is initiated with aciclovir.

Table I. Aetiology of aseptic meningitis and encephalitis by country

Causative organism	Proportion of cases (%)						
	US (1950-1981)[11]	South Africa (1981-1984)[12]	South Africa (1981-1989)[13]	Great Britain (1978-1982)[14]	Finland (1980)[15]	Finland (1966-1980)[16]	Finland (1973-1977)[17]
Aseptic meningitis							
Enterovirus (total)	66.7	75	91	52.3	33	39.2	Not studied
coxsackieviruses	12.1	12	15	11.8	24	39.2	
echoviruses	9.1	63	52	40.5	9	0	
unclassified	45.5	0	24	0	0	0	
Mumps virus	21.2	25	9	21	27	0	
Varicella zoster virus	0	0	0	2.8	3	4.2	
Cytomegalovirus	0	0	0	0	2	0	
Herpes simplex virus	3	0	0	8.5	0	0	
Adenovirus	0	0	0	33.7	2	4.2	
Measles	0	0	0	2.9	0	2.2	
Arboviruses	9.1	0	0	0	0	0	
Influenza virus	0	0	0	17.7	0	0	
Mycoplasma pneumoniae	0	0	0	2.2	0	0	
Influenza	0	0	0	0	0	0	
Other	0	0	0	5.3	0	0	
Unknown	0	0	0	0	33	50	
Encephalitis							
Mumps virus	20.7	Not studied	Not studied	Not studied	44	67.7	8.4
Enterovirus (total)	17.2				0	1.5	2.1
coxsackieviruses	6.9				0	0	0
echoviruses	6.9				0	1.5	0
unclassified	3.4				0	0	2.1
Varicella zoster virus	0				0	0	25.3
Cytomegalovirus	0				0	0	0
Herpes simplex virus	13.8				11	1.5	7.4
Adenovirus	0				0	4.4	2.1
Arboviruses	41.5				11	0	0
Mycoplasma pneumoniae	0				11	0	1
Influenza virus	3.4				0	2.9	3.2
Measles	0				0	1.5	4.2
Rubella	3.4				0	0	2.1
Parainfluenza	0				0	0	2.1
Respiratory syncytial virus	0				0	0	1
Other	0				0	0	1
Unknown	0				22	19.1	1

has a tri-modal distribution, with the largest number of cases occurring in neonates, followed by children under the age of 10 years, and by individuals between the ages of 30 and 40 years. However, the incidence of meningitis and encephalitis infections is influenced by a number of factors, which are discussed in more detail in the following section.

1.3.1 Influence of Immunisation Practices and Regional Variation

Although evident only through long term studies, factors such as climate and immunisation practices result in significant variations in the incidence and epidemiology of enteroviral CNS infections. Additionally, even within a given country, there are

Table II. Procedures reported after hospital admission for enteroviral meningitis (reproduced from Parasuraman et al.,[22] with permission)

Procedure	Frequency (%)[a]
Lumbar puncture	71.8
Computed tomography scan of the head	11.5
Magnetic resonance imaging of the brain	3.0
Antibacterial injection	2.5
Electroencephalogram	2.1
Electrocardiograph monitoring	1.0
Diagnostic ultrasound – heart	1.0

a Procedures were truncated at a frequency of less than 1%.

regional variations in the incidence and causality of enteroviral CNS infections. For example, a study of aseptic meningoencephalitis in Israel documented a nearly 2-fold variation in the incidence among different regions studied over a 2-year period.[8] In 1 year alone, the incidence of regionally reported cases of enteroviral meningitis in the US varied nearly 20-fold.[5,6,9] In the absence of a widely distributed reporting network, such variations lead to an inaccurate estimate of true incidence and aetiology of disease.[10]

The impact of immunisation practices on the epidemiology and incidence of CNS viral infections is clearly evident for mumps virus and poliovirus. A more descriptive breakdown of causative agents by country reporting aseptic meningitis is presented in table I. In countries where active vaccine prevention programmes for viral agents exist, the incidence of meningitis due to enteroviral causes have fallen dramatically. For example, following the introduction of the polio vaccine, no cases of poliovirus-associated meningitis were identified in Finland.[17] Coincident with the decreasing incidence of poliovirus, the nonpolio enteroviruses (coxsackieviruses groups A and B, echoviruses and numbered enteroviruses) became the primary causes of enteroviral meningitis, increasing from 12 to 46% worldwide. Today, on the eve of the realisation of the goal of global eradication, in the overwhelming majority of the world poliovirus rarely accounts for cases of enteroviral meningitis or myelitis. However, in regions where eradication of poliovirus has not yet occurred, these agents may continue to contribute significantly.

1.3.2 Influence of Diagnosis and Reporting

Diagnostic techniques to identify enteroviral agents in clinical specimens are continually evolving. Pre-molecular era reports of the incidence and epidemiology of enteroviral CNS infections are limited by the traditional diagnostic modalities of enteroviral culture and serology. Viral culture is significantly less sensitive than newer molecular-based diagnostic assays such as PCR (and enterovirus-PCR) for the diagnosis of enteroviral and herpes simplex infections of the CNS.[2,3,18] Therefore, conclusions regarding the epidemiology and incidence of CNS enteroviral infections that are based on older methodologies may lead to an underestimation of their true values.[18]

1.3.3 Influence of Seasonal Variation

Although aseptic meningitis occurs sporadically throughout the year, its incidence peaks during the summer and early autumn (fall) months in the Northern Hemisphere.[19] Seasonal outbreaks of aseptic meningitis are also reported in Japan and Australia.[20,21]

Table III. Major resource categories used during treatment for enteroviral meningitis (reproduced from Parasuraman et al.,[22] with permission)

Resource	Description
Physician visit	A patient's visit to a physician's office or clinic
ER visit	Admission to ER for suspected enteroviral meningitis
Hospital admission	Admission to hospital for suspected enteroviral meningitis
Medication	Intramuscular or intravenous aciclovir (acyclovir)
Procedure	Includes lumbar puncture, computed tomography scan of the head, magnetic resonance imaging of the brain, injection of antibacterial, electroencephalogram and other procedures performed at the physician's office, ER or hospital
Re-hospitalisation	Re-admission of a patient to the hospital
Follow-up physician visits	Visit of a patient to the physician's office after an initial office visit, ER visit or hospitalisation due to enteroviral meningitis

ER = emergency room.

2. Costs

2.1 Direct Costs

The direct costs of medical management of enteroviral meningitis are consequent to resource utilisation for symptom alleviation. The major resources that contribute to the overall direct cost of management of enteroviral meningitis include physician visits, hospital admissions, emergency room (ER) visits, medications, procedures such as lumbar puncture and CT scans, re-hospitalisations and follow-up physician visits.[22] Depending on the clinical presentation, the patient may be sent home on supportive medications from the point of initial presentation (a physician's office, ER or hospital) or be referred to the ER and/or admitted to a hospital for further evaluation and care.

The monetary valuation of the resources is dependent on the accounting system used. In addition, the calculations of the direct costs are also influenced by the perspective of the analysis. For example, the direct 'costs' to a payer reflect the 'charges' (or costs plus profits or losses) by the institution providing care. A listing of the most common procedures performed is provided in table II. A listing of typical resource categories during the management of enteroviral meningitis is provided in table III. A breakdown of estimated costs by course of management of enteroviral meningitis is provided in table IV.

Table IV. Valuation by age group of major resource categories used during treatment for enteroviral meningitis (reproduced from Parasuraman et al.,[23] with permission)

Resource category[a]	Cost ($US) [1996 values]	
	adult	paediatric
EAB	79	79
ER, LP, HOSP, COMP	20 443	11 826
ER, LP, HOSP, UNCOMP	5 235	5 151
ER, LP, NOHOSP	974	724
ER, NOLP	505	931
INHOSPLP, HOSP, UNCOMP	4 245	4 639
INHOSPLP, NOHOSP	174	121
INHOSPLP, HOSP, COMP	10 363	10 916
INHOSPNOLP, HOSP, COMP	12 164	6 828
PNOLP, HOSP, UNCOMP	3 455	4 224
IVA[b]	141 or 424	141 or 424
MD	40	34
Readmit	12 200	12 200
Repeat MD	40	34

a The data represent the costs of patients undergoing different levels of care. For instance ER, LP, HOSP, COMP represents the costs of patients admitted to the ER with enteroviral meningitis, LP performed in the ER, patient requiring hospitalisation with a complicated course of hospital stay.

b Estimated from the Drug Topics Red Book.[24] For ER, LP, NOHOSP, cost of IVA = $US141; for all other nodes, cost of IVA = $US424.

COMP = complicated hospital course; **EAB** = empirical antibacterial in physician's office or ER (ceftriaxone 2g intramuscularly); **ER** = emergency room; **HOSP** = hospital stay; **INHOSPLP** = LP performed in hospital; **INHOSPNOLP** = LP not performed in hospital; **IVA** = intravenous antibacterial in ER or hospital (intravenous ceftriaxone 2g every 12 hours for 3 days); **LP** = lumbar puncture; **MD** = physician office visit; **NOHOSP** = no hospital stay; **NOLP** = lumbar puncture not performed; **Readmit** = readmission to hospital; **UNCOMP** = uncomplicated hospital course.

A Medline search was conducted for the years 1985 to 2000, using the key words 'viral or aseptic meningitis' and 'cost or economic or resource use'. A total of 24 citations were returned, of which 5 studies presented cost data and were pertinent to this review. In addition, we reviewed 2 additional relevant articles obtained through cross-references, and knowledge of recent submissions. A brief review of the relevant papers is presented in table V. In the studies by Rice et al.,[5] Marshall et al.,[25] Wall et al.,[27] Elmore et al.[26] and Waisman et al.,[28] the cost estimates were based on patient discharges with a diagnosis of enteroviral meningitis. Thereby, the valuation is essentially a reflection of hospitalisation costs.[5,22,27,29] A more comprehensive valuation has been reported using a decision model.[30] However, the decision-analysis model utilised multiple sources of data in the cost estimation process in order to account for the entire course of management (i.e. physician office, ER or hospital). This utilisation of multiple sources for cost estimation may lead to a larger variation in the valuation of the resources because of the use of different cost accounting systems.

Rice et al.[5] reviewed all cases (n = 440) of aseptic meningitis reported to the Rhode Island Department of Health during the outbreak of 1991 (May to October). However, they were able to obtain the billing records for inpatient and outpatient man-

Landscape Table V to go here

agement for only 103 patients. Rice et al.[5] applied institution-specific cost-to-charge ratios to compute the cost of providing care. Patient ages ranged from 8 weeks to 74 years (mean age 17 ± 13.7 years) with 55% (n = 224) of patients below 18 years of age. The average hospital stay for all inpatient management (n = 324) was 61 ± 34 hours. 35 patients were not admitted and were provided with outpatient care. Although not specifically stated by the authors, it is assumed that choice of inpatient or outpatient management was driven primarily by patient presentation. The average cost of inpatient management during this outbreak was $US1757 ± $US198. This was 3-fold higher than the $US450 ± $US63 cost for outpatient management (1991 values).

Marshall et al.[25] followed all patients less than 18 months of age admitted to the hospital during September and October of 1996 for 'rule out sepsis', undifferentiated febrile illness or suspected meningitis. They collected CSF and reviewed hospital charts to obtain demographic, total hospital days, afebrile days and hospital charges. They identified 18 of 51 patients with pleocytosis upon examination of the CSF and who were eligible for further diagnosis of enteroviral meningitis by PCR. Marshall et al.[25] reported 9 patients to be PCR positive and 9 patients to be PCR negative for enterovirus. The 18 patients had a combined hospital stay of 79 days for total charges of $US91 689 with mean [± standard deviation (SD)] charges of $US5093 ± $US3554 per patient. The PCR-positive patients had mean (± SD) charges of $US4921 ± $US1674, whereas PCR-negative patients had mean (± SD) charges of $US5266 ± $4897 (1996 values).

Wall et al.[27] conducted a retrospective analysis of the top 10 diagnoses for admission at their institution over the period of 1990 to 1994. Six diagnoses for which administrative data were available were included for further analysis: asthma (n = 1983), bronchiolitis (n = 692), gastroenteritis (n = 733), 'rule out sepsis' (n = 1065), urinary tract infection (n = 516) and enteroviral meningitis (n = 288). Patients were included in the analysis if they were hospitalised over the time period and were less than 18 years of age. All patients were discharged either

Table V. Review of published papers reporting resource use in enteroviral meningitis

Reference	Study design	Setting	Methods	No. of patients	Age (y) [mean ± SD]	Resources identified	Resources valued	Perspective identified	Discounting	Sensitivity analysis	Mean cost per patient ($US) [year of costing]
Rice et al.[5]	R, O	H	CA, PB	408	17 ± 13.7	No	Yes	I, Pr	NA	No	Inpatients 1757 ± 198; outpatients 450 ± 63 [1991]
Marshall et al.[25]	P, O	H	CA, PB	53	0.19 ± 0.14	No	Yes	I, Py	CPI	No	5093 ± 3554 [1996]
Elmore et al.[26]	R, O	H	CA, PB	168	NR	No	No	No	No	No	NR
Wall et al.[27]	R, O	H	CA, PB	288	NR	No	Yes	I, Py	No	No	2824 [1990]
Parasuraman et al.[22]	R, O	H	CA, PB	30 087	NR	Yes	Yes	I, Py	No	No	8292 ± 14 690 [1996]
Parasuraman et al.[23]	DA, M	PO, ER, H	DM	NA	NA	Yes	Yes	Yes, Py, S	NA	Yes	Adults 4531 ± 150, paediatric 4971 ± 111, 5-7 ARDs per episode[1996]
Waisman et al.[28]	R, O	ER, H	CS	158	4.7 ± 3.5	No	No	I, Pr	NA	No	875[a] [1999]

a Calculated as 3.5 days of hospitalisation × $US250 per day.

ARDs = activity-restricted days; **CA** = cost aggregation; **CS** = cost saving; **CPI** = Consumer Price Index deflation; **DA** = decision analysis; **DM** = decision model, modified Delphi, Monte Carlo simulation; **ER** = emergency room; **H** = hospital; **I** = inferred, not stated; **M** = modelling; **NA** = not applicable; **NR** = not reported; **O** = observational; **P** = prospective; **PB** = patient billings; **PO** = physician office; **Pr** = provider; **Py** = payer; **R** = retrospective; **S** = societal; **SD** = standard deviation.

by a paediatrician or a subspecialist. International Classification of Diseases (ICD-9) codes were used to classify patients and 2 physicians reviewed the records to code the status of the admission as complicated or noncomplicated. Wall et al.[27] reported mean charges for hospital admissions with enteroviral meningitis in 1990 US dollars to be $US2824, with significantly greater charges for a complicated admission as compared with noncomplicated admission ($US4177 complicated *vs* $US2580 noncomplicated, $p < 0.001$). The Wall et al.[27] study indicates that since the resource expenditures were incurred at the same single institution, charges were a reasonable proxy for the costs of providing care at their institution. This report provides a comparison of mean charges for enteroviral meningitis with those for selected other hospital admissions during the same time, including those for asthma ($US4899), bronchiolitis ($US5763), gastroenteritis ($US3143), 'rule out sepsis' ($US2859) and urinary tract infection ($US4003). Thus, at this institution, a complicated hospital admission for enteroviral meningitis may be similar in charges to admissions for urinary tract infection, asthma or bronchiolitis, whereas a noncomplicated admission for enteroviral meningitis may be similar in charges to those for 'rule out sepsis' and gastroenteritis.

Elmore et al.[26] conducted a retrospective review of 171 episodes (168 patients) over a 2-year period. Medical records of patients with a diagnosis of meningitis or encephalitis in the emergency department were evaluated, and in addition all hospital discharges with an ICD-9 code that could possibly represent acute meningitis were also evaluated. Patient records were then evaluated and those with a CSF leucocyte count $>5/10^6$/L and a CSF Gram stain negative for bacteria were further evaluated. The majority of patients (53%) were between 17 and 60 years of age, with 28% of patients less than 6 years. Hospitalisation occurred in 70% of the cases, with 83 patient episodes (49%) requiring a CT scan or MRI of the brain. Empirical antibacterials were administered to 51% of patients, predominantly to the youngest age group (79% of those <6 years). Elmore et al.[26] do not report the episodes in terms of costs or charges and therefore it is difficult to compare the economic value of the resources consumed with the other reports. However, the resource use patterns are comparable with those in the other reports.

Waisman et al.[28] followed 158 patients aged 3 months to 18 years presenting to their institution during the Israel outbreak between March and December 1993. All diagnoses of enteroviral meningitis were confirmed by lumbar puncture. Of the 158 patients, 59 (37.3%) were discharged directly from the ER. The presentation characteristics, hospital stay and costs between these 2 groups were compared. Younger patients were typically hospitalised (mean age 4.7 *vs* 5.7 years, $p < 0.05$), and the hospitalisation rate was higher during the evening and night shifts compared with the day shift (66.7 *vs* 51.5%, $p < 0.05$). Headache and excessive vomiting were the most common symptoms reported in both groups; however, the incidence of both symptoms were significantly higher in the hospitalised group (headache 85.7 *vs* 54.7%, excessive vomiting 69.7 *vs* 38.2%). The hospitalised patients also reported significantly greater irritability (8.1 *vs* 1.8%, $p < 0.05$). All other typical signs and symptoms were similar between the 2 groups, including a mean presentation with illness of 1.5 days. Based on the mean duration of hospitalisation of 3.5 days, cost for 1 day of hospitalisation of $US250, and fixed cost of ER admission of $US105, Waisman et al.[28] estimated a cost saving of $US145 per day of early discharge from the hospital. Thus, during the outbreak of 1993, Waisman et al.[28] estimated a cost saving of $US51 625 to their centre for the 59 patients discharged from the ER (1993 values).

Parasuraman et al.[22] have separately reported a secondary database analysis of all state discharges for 3 populous states in the US, and an analysis using the 1996 Pennsylvania Medicaid. This analysis describes patients discharged with a diagnosis of enteroviral meningitis (ICD-9 code 047.xx). The pooled analysis of over 30 000 patients indicates a mean hospitalisation of 4 days and a mean charge of $US8300 per admission (table VI). Valuation of

major resource categories by age group from the Medicaid data set is provided in table IV.

2.2 Indirect Costs

Indirect costs include nonmedical and intangible costs that are incurred as a result of the disease or its treatment. These costs can be accounted as 'time costs' or costs incurred from the morbidity caused by the disease. These typically include: (i) costs related to the treatment that involve time spent by the patient or family (e.g. travel costs); (ii) costs associated with impaired ability to work or do leisure activities due to morbidity; (iii) costs associated with lost productivity due to death; and (iv) costs associated with the decrement in quality of life due to the illness. Since indirect costs include those costs that are beyond those 'spent' for medical management, inclusion of this assessment provides a comprehensive estimation of the economic impact. Typically, indirect costs must be included in any analysis that estimates the economic impact from the societal perspective.[31] Although it is more difficult to estimate indirect costs, several different methods have been proposed for their valuation.[32]

We identified only one evaluation that estimated indirect costs for enteroviral meningitis.[2] The estimation assigned the amount of time that patients with the disease miss from school, work or leisure activities in terms of activity-restricted days (ARDs). Using a modified Delphi technique, participants (a panel of 7 expert physicians) were asked to estimate the average time patients with enteroviral meningitis spend away from school, work or leisure activities. The panel estimated that for each episode of enteroviral meningitis, patients incur 5 to 7 ARDs. No assessment of the quality-of-life impact was made. Although not specifically reported, one method to assign a monetary value to the ARDs would be to multiply the total estimated number of ARDs by the median income reported for the year.

The costs of managing chronic adverse drug or disease effects (such as neurological sequelae) and death should be considered in calculating indirect costs; however, the rarity of these events in enteroviral meningitis preclude any meaningful estimation of these costs and have not been reported in the literature.

3. Outcomes

3.1 Neurological Sequelae and Death

Rare reports of neurological sequelae have been reported in the literature, including paresis or paralysis, papilloedema and cranial nerve palsies, and decreased receptive language functioning.[29,30,33-35] However, recent reports on the long term sequelae of enteroviral nonherpes meningitis, including surveillance reports, are not supportive of these neurological sequelae. Overall, nonherpes enteroviral meningitis rarely results in death.

3.2 Hospitalisations

Overall, approximately one-third to half of the patients presenting to a physician's office or ER with suspected enteroviral meningitis are hospitalised. The decision to hospitalise is driven by several factors, including patient presentation, time of

Table VI. Mean length of stay and mean charges for hospital discharges due to enteroviral meningitis by data source (reproduced from Parasuraman et al.,[22] with permission)

Source	Number[a]	Mean (± SD) length of stay (days)	Mean (± SD) charges ($US) [1996 values]
California	15 559	3.89 ± 4.72	8826.21 ± 17 341.50
Florida	9 382	4.19 ± 4.14	8177.56 ± 11 391.30
Illinois	5 146	3.95 ± 3.63	6887.37 ± 10 766.80
Pooled[b]	30 087	3.99 ± 4.37	8292.32 ± 14 690.38

a The numbers reflect specific International Classification of Diseases (ICD-9) codes for enteroviral meningitis (047.XX), which may not reflect the true incidence of enteroviral meningitis in a typical healthcare system.

b Data for the 3 states were pooled to obtain summary information.

SD = standard deviation.

presentation, age of patient and access to medical care. In general, poor clinical presentation, evening or night presentation, younger age of patient and limited access to medical centres are motivators for hospitalisation. In the case of children, it is more common to hospitalise for observation and/or to initiate empirical antimicrobial therapy.

4. Discussion

Management of enteroviral meningitis imposes a sizeable economic burden both from the payer and societal perspectives. Reports on the incidence of enteroviral meningitis vary from approximately 30 000 hospitalised cases to over 2 million cases of aseptic meningitis per year.[7,36] Using an estimate of 300 000 annual cases of aseptic meningitis in the US, the cost impact would approximate $US2 billion in direct costs alone.[30] Assuming 5 ARDs per episode, the additional economic burden in terms of indirect costs to society would approximate 1.5 million ARDs annually in the US. Utilising the median income of full-time workers in the US as an estimate of the additional impact in terms of lost productivity in the full-time employed population, the productivity loss would range from $US680 to $US910 per episode of enteroviral meningitis.

The studies reviewed for this paper used different methodologies, designs and accounting systems, which makes it difficult to compare resource use and costs across studies. However, it appears that hospitalisations (and re-hospitalisations) are the single largest cost drivers in the overall management of enteroviral meningitis. It appears that there are primarily 2 drivers of the decision to hospitalise patients who present for medical management: (i) to rule out bacterial infection; and (ii) to treat patient dehydration caused by excessive nausea and/or vomiting. Interventions that are aimed at faster detection of the (viral) cause, or reduce the need for or duration of hospitalisation, will significantly impact the direct cost of management of the episode. For instance, early detection of viral cause has led to significantly fewer ancillary tests, shorter duration of antibacterial use and shorter hospital stay.[37] Interventions that reduce or mitigate the course of the illness will contribute significantly to patient well-being and impact indirect costs. Potential direct medical cost savings from use of an effective agent after hospital admission will stem from reduction in severity and duration of symptoms and reduction in length of stay. Potential indirect medical cost savings will stem from reductions in time to return to work, school and normal leisure activities.

Currently, there is no accepted treatment for non-herpes enteroviral meningitis, other than supportive care and selective use of empirical antibacterials until a bacterial aetiology has been excluded. Several compounds are in various stages of development for the management of enteroviral meningitis.[38] The most advanced agent in terms of clinical development at this time is pleconaril.[39] Preliminary results suggest a clinical benefit in both children and adults. Pleconaril was associated with a 38 to 50% improvement in symptoms in children, with improvement noted as early as 24 hours after initiation of therapy.[40] Similarly, pleconaril treatment resulted in a 2-day reduction of meningitis symptoms and an earlier return to work/school in adults.[41] Although the economic and humanistic impact of pleconaril has not been prospectively studied, the availability of effective agents is likely to influence medical management and, in turn, the burden of enteroviral meningitis and the impact of interventions on that burden.

5. Conclusions

Enteroviral meningitis causes significant patient morbidity and economic burden. Interventions that will improve early diagnosis or decrease the duration of illness and need for hospitalisation will significantly impact the cost of managing enteroviral meningitis. Additional prospective studies are needed to document patient well-being and estimate the indirect cost of enteroviral meningitis.

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