The high burden of hospitalizations for primary EBV infection: a 6-year prospective survey in a French hospital

L. Hocqueloux[1], X. Causse[2], A. Valery[3], J.-C. Jandali[7], O. Maitre[4], C. Soin[5], J. Buret[1], F. Ouane[1], M. Niang[1], C. Mille[1], T. Prazuck[1], J. Guinard[6] and A. Guigon[6]

1) *Service des Maladies Infectieuses et Tropicales,* 2) *Service d'Hépato-Gastro-Entérologie,* 3) *Département d'Information Médicale,* 4) *Service d'Accueil des Urgences,* 5) *Service d'Oto-Rhino-Laryngologie,* 6) *Laboratoire de Microbiologie, CHR d'Orléans—La Source and* 7) *Service de Pédiatrie, CHR d'Orléans—Porte Madeleine, Orléans, France*

Abstract

Primary Epstein-Barr virus infection (PEI) is acquired increasingly later in life in developed countries, involving a growing number of adults. No studies have examined the effect of age on PEI. We conducted a prospective, single-centre, noninterventional survey to assess the clinical and economic effects of PEI care according to age. We included all serology-confirmed cases observed in all departments of a large regional hospital. Clinical and biologic data, therapeutics and costs of care were examined. Over a 6-year period, we included 292 subjects (148 children and 144 adults) with a median age of 15.4 years (range 9 months to 79 years). Adults were hospitalized more often (83% vs. 60%) and for longer periods of time (median 4 days vs. 2 days) than children ($p \leq 0.0001$ for both). Two adults required a secondary transfer into the intensive care unit, although no children did. Typically, adults showed higher levels of activated lymphocytes and liver abnormalities. They also required the use of systemic corticosteroids more often (45% vs. 23%, $p < 0.0001$) and for longer periods of time (median 7 days vs. 3 days, p 0.02) than children. Overall, the costs were significantly higher for adults than for children (median, €1940 vs. €1130, $p < 0.0001$), mainly because of the frequency and duration of hospitalizations. Age increases the immune response and clinical severity of PEI, resulting in substantial additional costs for the community. Better recognition of the disease in adults could shorten the average length of hospital stay.

Keywords: Adults, children, costs, primary Epstein-Barr virus infection, severity
Original Submission: 5 May 2015; **Revised Submission:** 7 July 2015; **Accepted:** 17 July 2015
Editor: L. Kaiser
Article published online: 29 July 2015

Corresponding author: L. Hocqueloux, Service des Maladies Infectieuses et Tropicales, CHR d'Orléans—La Source, BP 86709, 45067 Orléans Cedex 2, France
E-mail: laurent.hocqueloux@chr-orleans.fr

Introduction

In industrialized countries, there has been a shift for several decades in the age of acquisition of Epstein-Barr virus (EBV) from early childhood to adolescence or even adulthood [1–4]. Several seroepidemiologic studies have consistently linked this shift to the overall improvement of the economic level and sanitary conditions of the populations concerned [4–7]. Meanwhile, an increase in the frequency of hospitalizations for primary EBV infection (PEI) has been reported [1,8].

PEI in young children is often asymptomatic or manifests as a mild and nonspecific illness, whereas most adolescents and adults present with a typical infectious mononucleosis syndrome [3,9]. In a large prospective study conducted in the early 1990s, up to 85% of young adults with suspected infectious mononucleosis were hospitalized [10]. Moreover, a growing incidence of severe (and sometimes life-threatening) forms of infectious mononucleosis in apparently immunocompetent adults has been reported by some authors [8,10–12].

http://dx.doi.org/10.1016/j.cmi.2015.07.015

Here we report on a prospective observational survey that we conducted to assess how age affects the severity of PEI and its costs in a French hospital.

Patients and Methods

Study design and setting

This study was a prospective, noninterventional survey in a large (1250 beds) tertiary-care centre in France. From 2008 to 2013, we systematically identified in- and outpatients who presented at our hospital with a suspicion of PEI by means of a triple-alert system, which includes physicians, laboratories and an electronic database. Physicians from all departments and biologists were asked to report any suspected case of PEI to the investigators (i.e. patients presenting with a classic triad or any other feature compatible with a viral infection together with activated lymphocytes on the blood count). Last, an electronic database system identified patients coded with PEI as a main or associated diagnosis (B27.0) according to hospital discharge codes.

The patients provided their consent to participate after being orally informed of the study protocol. This study was approved by the Orléans Hospital ethics committee.

Participants

Data from all suspected cases were collected soon after the patient's discharge (so as not to influence the physician's clinical findings, diagnosis, decisions of care or therapeutics) and reviewed by the scientific committee. Cases were definitely validated (and kept for analyses) if they met the following definition: clinical feature suggestive of PEI (as asserted by a physician's diagnosis) together with biologic evidence of acute EBV infection, i.e. positive IgM anti-VCA (with or without IgG) and negative IgG anti-EBNA antibodies (enzyme immunosorbent assay; Liaison, DiaSorin, Saluggia, Italy) or a positive EBV PCR result in whole blood in the absence of anti-VCA and anti-EBNA antibodies (real-time PCR; EBV R-gene, bioMérieux, Marcy l'Étoile, France).

Outcomes

The primary end point was to compare the clinical severity of PEI in a paediatric setting (i.e. patients aged <15 years and 3 months, henceforth called children) vs. those in an adult setting (i.e. patients aged $\geq$15 years and 3 months, henceforth called adults) by means of their respective admission rates, duration of stay in the hospital, intensive care unit (ICU) transfers and death rates. Secondary end points were used to describe how age affected the clinical and laboratory findings, therapeutic options and costs of care. Last, we aimed to identify factors predicting increased severity during PEI, which was assessed by the hospitalization rate and duration of stay.

Covariates

All (written or electronic) clinical, biologic, radiologic and therapeutic data were reviewed, summarized and anonymously computerized in a standardized form for analysis. The baseline data (i.e. at the time of hospital admission) included the following: demographic data, medical history, and clinical and laboratory findings. The follow-up data included the following: all reported clinical events until hospital discharge, therapeutic drugs used and any invasive therapeutic or diagnostic procedures.

The costs of hospital stay were estimated using the French Diagnosis Related Groups method. The diagnoses and procedures were encoded by the physicians at hospital discharge and were adjusted on the basis of the length of stay. All PEI cases were recalculated using the 2008 algorithm; then costs were standardized at the claim level to 2014, using an actualization rate of 4% per year, as recommended by French guidelines.

Statistical analysis

The data were expressed as median (interquartile range (IQR)), mean ± standard deviation or percentage values. Between-group differences were compared by the chi-square or Fisher's exact tests for categorical variables and the unpaired *t* test, Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables. Associations between outcomes of interest and various factors were tested by a multivariate logistic regression analysis. All p values were two tailed, and significance was set at the 0.05 level.

Results

Participants

Over a 6-year period (2008–2013), 292 cases of PEI were included comprising 148 children (51%) and 144 adults (49%) (Fig. 1). Overall, there were 155 male (53%) and 137 female (47%) subjects. The annual incidence was stable over time. The median age of the patients presenting with PEI was 15.4 years (IQR 5.1–21.4), ranging from 9 months to 79 years, and was stable over time. The main ethnic population was white (87.2%), followed by North African (7.1%), sub-Saharan African (5.3%) and Asian (0.4%) populations. Overall, 208/292 (71%) of all people presenting with PEI at our establishment were hospitalized for a median of 3 days (IQR 2–5). The hospitalization rate was stable over time.

Main outcomes

Overall, adults presenting with PEI were more likely to be hospitalized than children: 83% vs. 60% ($p < 0.0001$). Moreover,

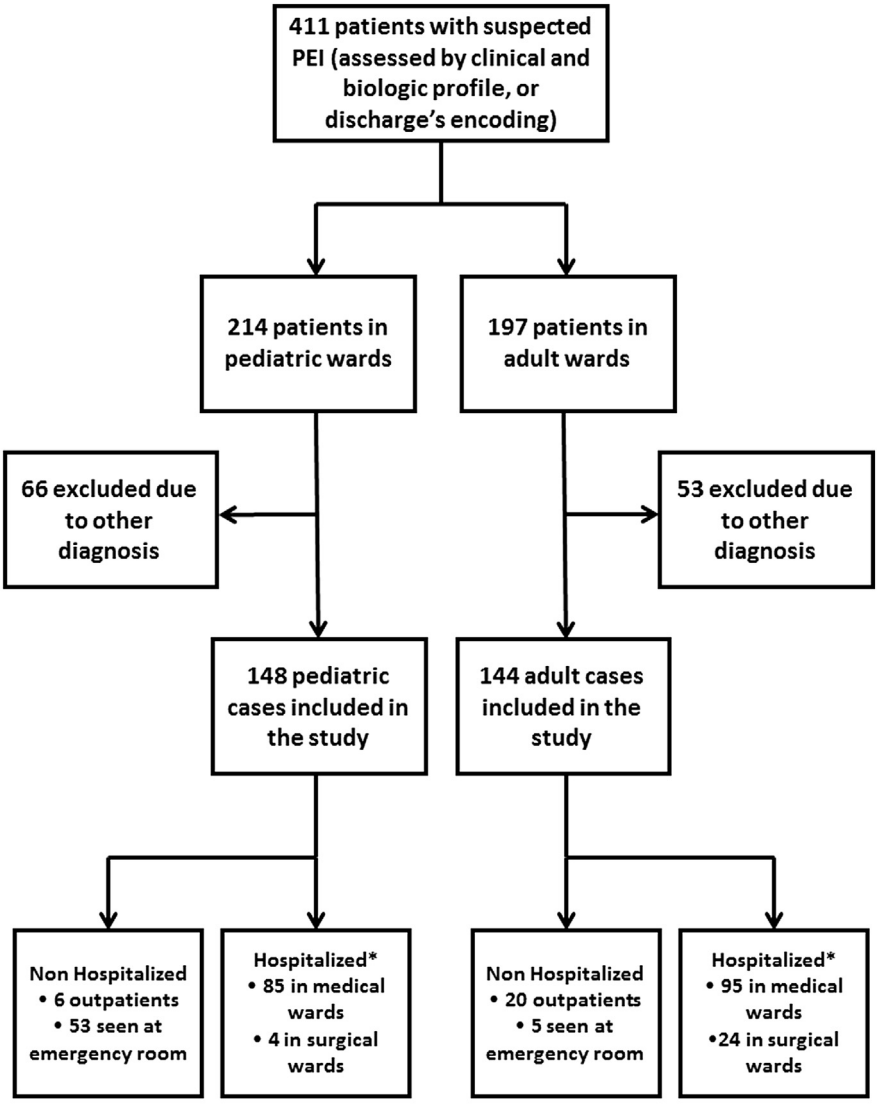

FIG. 1. Flow chart of patients with primary Epstein-Barr virus infection included in the survey.

adults who were hospitalized had a longer duration of stay (median 4 days, IQR 2–5) than children (median 2 days, IQR 1–4; p 0.0001). Two adults required a secondary transfer into an ICU (a 75-year-old woman with life-threatening hemophagocytic lymphohistiocytosis (HL) and a 28-year-old woman with acute myocarditis, neither of whom had previous debilitating conditions), whereas ICU transfer did not occur among children (p 0.2). One of these adults died from multiple organ failure complicating untreatable HL; there were no deaths among children (p 0.5).

Secondary outcomes

The main clinical and laboratory characteristics of the patients at hospital venue are summarized according to age group in Table 1. Notably, two patients had only immunosuppressive conditions before PEI (HIV infection in a child and ankylosing spondyloarthritis treated by adalimumab in a woman).

Clinical findings

Overall, the patients presented to our hospital a median of 6 days (IQR 4–9) after the onset of symptoms. The most frequent complaints and signs are summarized in Table 1. Although the classic triad (fever, sore throat and lymphadenopathy) was equally balanced between children and adults (63 vs. 68%, p 0.8), children were more likely to have nonspecific findings (i.e. rash, cough, diarrhea, runny nose, dehydration and convulsions) and to be nonwhite (Table 1). Conversely, adults

TABLE 1. Baseline characteristics of patients with primary EBV infection

Characteristic	Child *n*	Child Value	Adult *n*	Adult Value	p[a]
Demographic data	148		144		
Age (years)		5.2 (2.4–9.8)		21.5 (18.5–25.1)	<0.0001
Male sex		54.1		52.1	0.81
Ethnicity				<0.0001	
White		77.9		96.5	
Other[b]		22.1		3.5	
Clinical findings[c]		148		144	
Time from first symptoms to hospital venue (days)		4 (3–8)		7 (5–13)	<0.0001
Symptoms					
Sore throat		77.7		81.3	0.47
Odynophagia		37.2		49.3	0.04
Intense fatigue		35.1		40.3	0.39
Flulike syndrome		6.1		45.8	<0.0001
Headache		13.5		32.6	<0.0001
Abdominal pain		20.3		20.1	1.0
Anorexia		9.5		12.5	0.46
Respiratory discomfort		9.5		4.2	0.10
Signs					
Fever (temperature >38°C)		93.9		88.2	0.10
Cervical lymphadenopathy		75.0		85.4	0.03
Pharyngitis		77.7		81.3	0.47
Axillary and/or inguinal lymphadenopathy		13.5		45.1	<0.0001
Vomiting		24.3		25.0	1.0
Rash		28.4		17.4	0.03
Splenomegaly		10.1		31.9	<0.0001
Cough		28.4		12.5	0.001
Runny nose		31.8		1.4	<0.0001
Hepatomegaly		4.1		21.5	<0.0001
Diarrhoea		19.6		4.9	0.0001
Eyelid edema		14.9		6.3	0.02
Weight loss		9.5		7.6	0.68
Jaundice		0.0		9.0	<0.0001
Laboratory findings in blood					
Blood cell count	148		144		
Neutrophils (cells/μL)		3620		2695	0.03
Total lymphocytes (cells/μL)		5910		5700	0.42
Percentage of atypical lymphocytes		2 (0–11)		14 (4–23)	<0.0001
Haemoglobin (g/dL)		12.5		13.9	<0.0001
Platelets (cells/μL)		197000		196500	0.09
Liver tests	85		133		
Aspartate aminotransferase (ULN)		1.3 (0.9–3.6)		3.6 (1.3–6.6)	0.0001
Alanine aminotransferase (ULN)		1.4 (0.6–3.2)		5.0 (1.9–8.6)	<0.0001
γ-Glutamyltransferase (ULN)		1.2 (0.3–3.2)		3.0 (1.3–6.1)	0.0001
Total bilirubin (ULN)		0.4 (0.3–0.7)		0.8 (0.4–1.3)	<0.0001
Other markers					
C-reactive protein (mg/L)	134		138	18 (7–33)	0.03
Procalcitonin (U/L)	59		10	0.32 (0.09–0.75)	0.65
EBV DNA virus load (log/mL)	6		50	4.6 (2.7–4.5)	0.18

Data are presented as median (interquartile range) or %.
EBV, Epstein-Barr virus; ULN, upper limit of normal.
[a]Mann-Whitney *U* test used for nonparametric continuous data, chi-square test for dichotomous data.
[b]North or sub-Saharan African or Asian.
[c]Reported are clinical findings documented in at least 5% of patients of one group.

were more likely to present with enlargement of the lymphoid organs (i.e. lymph nodes, spleen and liver), severe odynophagia and jaundice. Adults also more frequently had severe headache that led to the application of a lumbar puncture: 11/144 (8%) vs. 2/148 (1%) for children (p 0.01) (Table 2).

Although the groups shared similar patterns of reasons that led to hospitalization (fever, sore throat/odynophagia, rash, hepatitis, abdominal pain, headache, lymphadenopathy and vomiting were the most frequent), adults were more likely to be hospitalized because of headache and hepatitis (13% and 15% vs. 1% and 1% for children, p 0.001 and 0.0004, respectively), whereas children were more likely to be hospitalized because of fever (58% vs. 34%, p 0.0007) (Supplementary Table S1).

Laboratory findings

Compared to children, adults displayed substantially greater amounts of activated lymphocytes in blood and elevated liver test results (Table 1). Strong elevation in liver tests (i.e. greater than 10 times the upper limit of normal) was observed in 18%, 15% and 12% of adults for alanine aminotransferase, aspartate aminotransferase and γ-glutamyl transferase, respectively, compared to 6%, 1% and 2% of children ($p < 0.05$ for all comparisons). Nevertheless, no patients developed hepatic failure. There were also no incidences of severe and symptomatic neutropenia, anemia, thrombopenia or coagulation disorder, except for the adult who died in the ICU from multiple organ failure with diffuse hemorrhages.

Treatments

Overall, the patients received symptomatic care, and none of the patients were treated with antiviral drugs, according to national practices. The patients complaining of severe odynophagia were hydrated and fed intravenously until swallowing had improved. Additionally, these patients were given systemic corticosteroids (SCS). The second reason patients received SCS was intense fatigue. Typically, SCS were first administered intravenously for 1 to 3 days (for hospitalized patients) and then provided orally. The median dosage was 1 mg/kg/d (IQR 0.85–1) of prednisone. Adults were nearly twice as likely to receive SCS compared to children (45% vs. 23%, respectively, $p < 0.0001$), and they received them for a much longer duration (median of 7 days vs. 3 days, respectively, p 0.02). Antibiotics (mostly β-lactams and macrolides) were widely provided to children and adults (65% vs. 52%, respectively, p 0.02) although documented bacterial superinfections were uncommon in both groups (5.4% vs. 7.6%, respectively, p 0.5). The patients who had been treated with SCS did not have a higher rate of bacterial superinfection (5% vs. 9% if no SCS, p 0.3).

Costs of care

Overall, the costs per case of PEI were significantly higher for adults than children (median €1940, IQR €1310–2637 vs. €1130, IQR €72–1954, respectively, $p < 0.0001$). These results were mainly driven by the higher hospitalization rate and length for adults (Fig. 2). Indeed, the prices for an external consultation (€46) or venue to the emergency room (€72) were standardized regardless of age, and the costs per day of hospitalization were even higher for children than adults (median €676, IQR €603–809 vs. €584, IQR €506–739, respectively, p 0.003).

TABLE 2. CSF findings of 13 patients who underwent lumbar puncture

Patient no.	Clinical feature	Age (years)	Sex	Leukocyte count (cells/μL)	Lymphocytes (%)	Protein (g/L)	Glucose (mmol/L)	Lactates (mmol/L)	PCR EBV (copies/mL)
1	Brachial plexus neuritis	41	M	7	ND	0.47	3.4	1.3	187
2	Cerebellar syndrome	36	M	5	ND	0.38	3.4	ND	< 200
3	Meningeal syndrome	32	F	2	ND	0.37	2.9	1.5	ND
4	Meningeal syndrome	24	F	1	ND	0.24	3.4	ND	ND
5	Meningeal syndrome	24	F	6	ND	0.4	3.2	1.9	ND
6	Meningeal syndrome	23	F	1	ND	0.4	3.3	ND	ND
7	Meningeal syndrome	22	F	2	ND	0.2	3.4	1.3	ND
8	Meningeal syndrome	20	F	3	ND	0.24	3.2	ND	< 200
9	Meningeal syndrome	20	M	1	ND	0.33	4.5	1.4	ND
10	Polyradiculoneuritis	19	F	52	98	0.91	3.1	ND	< 200
11	Meningeal syndrome	18	M	76	100	0.25	4.0	ND	< 200
12	Meningeal syndrome	9	F	5	ND	0.14	3.1	1.2	ND
13	Cerebellar syndrome	3	F	0	ND	0.22	3.2	ND	ND
	Mean values	22		12	99	0.35	3.4	1.4	

CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ND, not determined.

Factors associated with clinical severity

In the logistic regression analysis, a high percentage of activated lymphocytes (≥20%, i.e. the highest quartile) and vomiting were predictive of being hospitalized (odds ratio (OR) 4.95, 95% confidence interval (CI) 1.37–17.96, p 0.01, and OR 3.93, 95% CI 1.09–14.14, p 0.01, respectively), whereas the absence of fever decreased the risk of hospitalization (OR 0.23, 95% CI 0.07–0.74, p 0.01) (Table 3).

Patients who were hospitalized stayed a median of 4 days. In the logistic regression analysis, factors predicting a long duration of stay (i.e. 4 days or more) at the time of admission were age (OR 1.58, 95% CI 1.15–2.17, p 0.005, per each increase of a

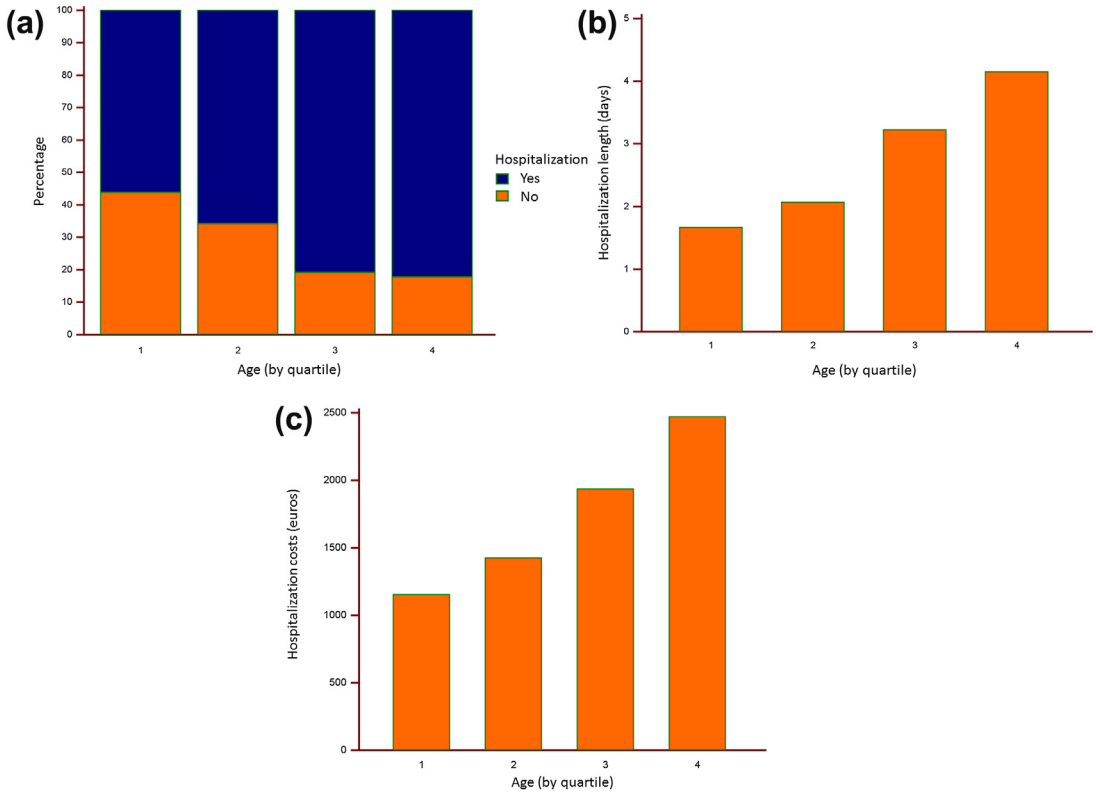

FIG. 2. Hospitalization rate, length and costs according to age (by quartile). Range for first quartile: 0.8 to 5.1 years; second quartile: 5.2 to 15.4; third quartile: 15.5 to 21.4; fourth quartile: 21.5 to 79.1. (A) Hospitalization disposition according to age. (B) Mean hospitalization length according to age. (C) Mean hospitalization costs according to age.

quartile), hepatomegaly (OR 2.93, 95% CI 1.11–7.75, p 0.03) and respiratory discomfort (OR 5.0, 95% CI 1.38–18.14, p 0.01) (Table 3).

Discussion

To our knowledge, our study was the first aimed at directly comparing children and adults presenting with PEI in a hospital setting. We found some evidence that the later in life EBV is acquired, the greater its clinical effect, because increasing age resulted in a higher hospitalization rate and longer duration of hospital stay.

In our experience, PEI was easily diagnosed in children, although their symptoms were often nonspecific. Conversely, PEI was less easily diagnosed in adults with complex clinical conditions; this difficulty may have led to a higher rate of hospitalization and diagnostic tools implemented. Typically liver damage was often overestimated in adults and led to numerous diagnostic procedures, although no liver failure was recorded. Such procedures may have lengthened the hospitalization of adults. However, older age obviously increased the immune-mediated antiviral responses and subsequently worsened the clinical condition. The symptoms of PEI are a result of the infiltration of lymphoid organs by specific activated cells towards EBV, combined with the release of proinflammatory cytokines by these cells [9]. These phenomena are directly related to the intensity of the EBV virus load and the anti-EBV-specific response [13]. We found that the percentage of activated lymphocytes not only positively correlated with patient age at PEI onset but also with the length of stay, intensity of liver abnormalities, enlargement of lymphoid organs (e.g. generalized lymphadenopathy, hepatomegaly and splenomegaly) and SCS use (data not shown). These findings suggest that the maturity of the immune system in adults certainly accounted for worse clinical symptoms. It has recently been reported that young adults with PEI share a similar transcriptomic signature with patients with HL, suggesting that EBV can cause uncontrolled and deleterious inflammatory responses [14]. Although HL is rarely observed during PEI, it is noteworthy that the only fatal case in our series was an adult who had developed complete HL.

During PEI, therapy is administered to treat symptoms because no antiviral drug has yet been shown to be effective [3,15]. It is noteworthy that antibiotics were provided to a majority of patients from both groups included in our study, even when a PEI diagnosis was identified. The main indication for therapy with antibiotics was the observation of any type of pharyngitis, although this condition is typically observed during PEI [9]. The use of SCS is also controversial. Although SCS are usually prescribed for the most symptomatic cases of PEI, a beneficial role has never been formally demonstrated in randomized trials [16]. In our study, SCS were widely prescribed to patients with severe odynophagia and intense fatigue; these symptoms occurred much more frequently in adults than in children. It is important to note that SCS had no deleterious effects on the risk of bacterial superinfection.

Except for two patients, all patients included in our study were healthy individuals without immune suppression. The adult patients with PEI were almost exclusively white, whereas a quarter of the children with PEI were born to nonwhite immigrant families. This result is in agreement with findings from the United States in which the socioeconomic environment strongly influences age at PEI acquisition [4,7].

In our experience, the incremental costs of PEI care in adults were mainly related to their more frequent and longer hospitalizations. We believe that a faster diagnosis of PEI would allow patients and doctors to be reassured of the benign nature of the condition, leading to outpatient monitoring, especially of liver involvement. Of note, longer hospitalization lengths were

TABLE 3. Factors associated with probability of being hospitalized for long-duration stay

	Risk of hospitalization				Risk of hospitalization ≥4 days			
Characteristic	**Univariate p**	**Multivariate p**	**OR**	**95% CI**	**Univariate p**	**Multivariate p**	**OR**	**95% CI**
Age (years)	<0.0001	—			0.0002	0.005	1.58[a]	1.15–2.17
Odynophagia	0.14	—			—	—		
No fever	0.03	0.01	0.23	0.07–0.74	—	—		
Vomiting	0.07	0.04	3.93	1.09–14.14	—	—		
Flulike syndrome	—	—			0.002	—		
Respiratory discomfort	—	—			0.06	0.01	5.0	1.38–18.14
Hepatomegaly	—	—			0.01	0.03	2.93	1.11–7.75
Jaundice	—	—			0.06	—		
Percentage of atypical lymphocytes	0.002	0.01	4.95[b]	1.37–17.95	0.006	—		
CRP (mg/L)	0.0002	—			—	—		
γ-Glutamyltransferase (ULN)	0.04	—			0.002	—		
Aspartate aminotransferase (ULN)	0.08	—			0.001	—		

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; ULN, upper limit of normal.
[a]Per each increase of quartile.
[b]For percentage ≥20%.

reported in other countries a decade ago: 7 days in the United States [17] and 9 days in Hungary [18].

The strength of our study is that it was a prospective survey that was conducted over several years in a single centre and exclusively included well-characterized PEI. Therefore, the management was homogeneous in time and place, which reinforces the validity of the differences we observed between adults and children. There are also some limitations. Our study only involved patients presenting to the hospital. Thus, a recruitment bias cannot be avoided considering that we recruited the most symptomatic cases requiring urgent and/or more intensive care, even if reasons that led to hospitalizations were obviously overestimated (in their severity), at least in some cases. Presumably the differences we found between adults and children would be much less marked for patients exclusively treated in the community.

PEI acquired during adulthood was obviously associated with a worsened condition that is likely related to the maturation of antiviral immune responses. Nevertheless, life-threatening visceral involvement was rare, even in an adult setting. A better recognition of the disease in adults, supported by rapid diagnostic confirmation, is expected to shorten hospital stays and substantially reduce the cost of care for the community.

Transparency Declaration

This work was supported by grants from the Centre Hospitalier Régional d'Orléans, France. The sponsor of the study had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; or the preparation, review or approval of the manuscript. No authors of this study have any financial or personal relationships with people or organizations that could inappropriately influence this work, although some authors (LH, XC, and TP) have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements, or consultancy fees.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.07.015.

References

[1] Morris MC, Edmunds WJ. The changing epidemiology of infectious mononucleosis? J Infect 2002;45:107–9.
[2] Takeuchi K, Tanaka-Taya K, Kazuyama Y, et al. Prevalence of Epstein-Barr virus in Japan: trends and future prediction. Pathol Int 2006;56:112–6.
[3] Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med 2010;362:1993–2000.
[4] Balfour Jr HH, Sifakis F, Sliman JA, Knight JA, Schmeling DO, Thomas W. Age-specific prevalence of Epstein-Barr virus infection among individuals aged 6–19 years in the United States and factors affecting its acquisition. J Infect Dis 2013;208:1286–93.
[5] Nye FJ. Social class and infectious mononucleosis. J Hyg (Lond) 1973;71:145–9.
[6] Crowcroft NS, Vyse A, Brown DW, Strachan DP. Epidemiology of Epstein-Barr virus infection in pre-adolescent children: application of a new salivary method in Edinburgh, Scotland. J Epidemiol Community Health 1998;52:101–4.
[7] Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in US children ages 6–19, 2003–2010. PLoS One 2013;8:e64921.
[8] Tattevin P, Le Tulzo Y, Minjolle S, et al. Increasing incidence of severe Epstein-Barr virus–related infectious mononucleosis: surveillance study. J Clin Microbiol 2006;44:1873–4.
[9] Odumade OA, Hogquist KA, Balfour Jr HH. Progress and problems in understanding and managing primary Epstein-Barr virus infections. Clin Microbiol Rev 2011;24:193–209.
[10] Grotto I, Mimouni D, Huerta M, et al. Clinical and laboratory presentation of EBV positive infectious mononucleosis in young adults. Epidemiol Infect 2003;131:683–9.
[11] Auwaerter PG. Infectious mononucleosis in middle age. JAMA 1999;281:454–9.
[12] Mellinger JL, Rossaro L, Naugler WE, et al. Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. Dig Dis Sci 2014;59:1630–7.
[13] Balfour Jr HH, Odumade OA, Schmeling DO, et al. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students. J Infect Dis 2013;207:80–8.
[14] Dunmire SK, Odumade OA, Porter JL, et al. Primary EBV infection induces an expression profile distinct from other viruses but similar to hemophagocytic syndromes. PLoS One 2014;9:e85422.
[15] Rafailidis PI, Mavros MN, Kapaskelis A, Falagas ME. Antiviral treatment for severe EBV infections in apparently immunocompetent patients. J Clin Virol 2010;49:151–7.
[16] Candy B, Hotopf M. Steroids for symptom control in infectious mononucleosis. Cochrane Database Syst Rev 2006;(3):CD004402.
[17] Borer A, Gilad J, Haikin H, Riesenberg K, Porath A, Schlaeffer F. Clinical features and costs of care for hospitalized adults with primary Epstein-Barr virus infection. Am J Med 1999;107:144–8.
[18] Almási I, Ternák G, Bali I. [Clinical aspects of the diagnosis and treatment of infectious mononucleosis in primary care and in departments of infectious diseases]. Orv Hetil 2001;142:899–903.