**Introduction**

Enterovirus and human parechovirus (EV/HPeV) are two viruses belonging to the same family of Picornaviridae. The clinical manifestations of HPeV infection are often indistinguishable from those caused by EV. Infections with these viruses are prevalent in children and generally cause mild upper respiratory and gastrointestinal illnesses.1 Over the past decades, large outbreaks of EV/HPeV had been documented worldwide.2 During these outbreaks, an increase in more severe illnesses, including sepsis like illness, myocarditis, pneumonia, myelitis and meningo-encephalitis has been reported.3,4,5 Unfortunately, there are no antivirals approved of the treatment of EV/HPeV and management remains mainly supportive.

In England and Wales, where the last EV/HPeV outbreak was due to echovirus 13 during 2000-01, we recently identified a year-on-year increase in reports of laboratory-confirmed EV cases across all age-groups, most likely because of increasing use of routine PCR-testing by hospital laboratories.6 At the same time, we also identified rare but severe cases of childhood EV/HPeV through our national surveillance of EV/HPeV meningo-encephalitis in young infants (<http://www.rcpch.ac.uk/bpsu/neoentero>), retrospective case-note review,7 and individual cases.8 In order to better define the burden of severe childhood EV/HPeV infections, we analysed data for all pediatric intensive care admissions in the United Kingdom and the Republic of Ireland during the five most recent calendar years.

**Methods**

The Paediatric Intensive Care Audit Network (PICANet) records core demographic and clinical details of the management of all critically ill children in pediatric intensive care units (PICUs) across the United Kingdom and the Republic of Ireland, using standardised data collection forms ([www.picanet.org](http://www.picanet.org)).

We requested anonymized data on all children aged 0-15 years, admitted to PICU in the UK and the Republic of Ireland between 01 January 2010 and 31 December 2014 with any one of the following recorded at any time during their admission: "enterovirus", "echovirus", "parechovirus", "picornavirus", "coxsackievirus" or "enteroviral". The final dataset had information on the month and year of admission, age (in days for neonates, in months for infants and in years for older children), gender, outcome (alive/dead), primary, secondary and subsequent diagnoses (codes and description), need for invasive ventilation (yes/no and duration), inotropes (yes/no and duration), renal hemofiltration (yes/no and duration) and extracorporeal membrane oxygenation (ECMO) (yes/no and duration). Data on clinical symptoms and signs, laboratory and microbiology test results, EV/HPeV genotype, medications (antivirals/steroids/immunoglobulin), radiological investigations or surgical procedures are not routinely recorded in the PICANet dataset.

**Results**

During 2010-14, there were 104 PICU admissions in <16 year-olds related to EV/HPeV in the UK and the Republic Ireland. The number of admissions increased three-fold over the five-year period, from 0.62/1,000 (n=12) to 1.8/1,000 (n=36) PICU admissions in 2010 and 2014, respectively. The male-to-female ratio was 1.6:1. Analysis of cases by month of year revealed a bimodal distribution, with peaks in June-July and October-November. The majority of cases were younger than 1 year (86/104, 83%), nine (9%) were one year-old and nine (9%) were two (n=5) years or older (n=4). Neurological presentations were most common (42/104, 40%), followed by respiratory (n=21, 20%), cardiac (n=17, 16%) and sepsis like illness (n=11, 11%). The remaining 13 children (13%) had non-specific clinical presentations (fever, collapse, etc.) [[**Table 1**](#Table1)]. Neurological presentation were more common in <3 month-olds (34/74, 46%) compared to older children (8/30, 27%), but the difference was not significant (P=0.069) [[**Figure 1**](#Figure1)].

The majority of children required invasive ventilation (80/104, 77%; median 5 days, range 1-49 days) and 40% (42/104) required inotropic support (median 5 days, range 1-48 days), while 4/98 children with available information (4%) needed renal hemofiltration (median 3 days, range 1-8 days) and three (3%) were severe enough to require ECMO (median 8 days, range 2 to 12 days). Eight children (8%) died during their stay in PICU, including two (1 cardiac presentation, 1 respiratory presentation) who had severe underlying neuro-developmental co-morbidities. Although there were only a few such cases, children with cardiac manifestations appeared to require more intensive care support and also more likely to die in PICU [[**Table 1**](#Table1)].

**Discussion**

We have attempted to define the burden of severe childhood EV/HPeV infections in the UK and the Republic of Ireland during a stable period when no outbreaks are known to have occurred. Over the five years of observation, there was a three-fold increase in EV/HPeV-associated PICU admissions, consistent with national trends, most likely because of increasing use of PCR-testing for these viruses in local hospitals.6 In 2014, EV/HPeV infections were associated with 1.8 per 1,000 PICU admissions, but this is likely to be a significant underestimate because it requires the diagnosis to be made whilst the child is still an inpatient in the PICU. PCR-testing for EV/HPeV is usually only performed in large hospitals and there, too, such tests are not performed on a daily basis. Hence, in a significant proportion of cases, the diagnosis would only be confirmed after PICU discharge. It is likely that case ascertainment will continue to increase as PCR-testing becomes more widely available and incorporated into routine clinical practice.

Our series of cases is unique in that it captures all clinical presentations to PICU caused by all different EV/HPeV types in a national setting over a 5-year period. Moreover, unlike much of the published literature, the cases were identified when there was no outbreak and, therefore, no particular EV/HPeV type dominated. Our findings indicate that infants account for the majority of children with EV/HPeV infections who require PICU admission. Most were extremely ill, often requiring multi-organ support. In particular, although there were only 17 children with cardiac presentations, nearly all required inotropic support. Moreover, two of the four children requiring dialysis, two of the three children requiring ECMO support and half the fatalities occurred in this group.

Rare but severe cases of HV/HPeV myocarditis are well-reported. In a recent case series from London, UK, five young infants with acute fulminant myocarditis presented with non-specific symptoms such as vomiting, cough and poor feeding to their local hospital, but rapid deterioration then prompted referral for intensive care.9 Two children died before the retrieval team arrived, while one of the three survivors needed urgent orthotopic heart transplantation. The authors recommended that myocarditis should be considered in any previously well child presenting with a viral prodrome and non-specific organ dysfunction associated with dysrhythmias, shock or acute heart failure, even without cardiomegaly. In another study, only 8/24 (33%) with enteroviral myocarditis requiring ECMO survived.10 Multisystem organ dysfunction, particularly with renal involvement, may portend a poor prognosis, highlights the importance rapid diagnosis to ensure early and appropriate supportive care.11

A limitation of our study is that PICANet does not collect extensive data on presenting symptoms or interventions other than those specified in the PICANET dataset. Another limitation to our study is that diagnosis may not be confirmed until after the children are discharged from PICU and that may substantially underestimate the true burden of EV/HPeV infections in children admitted to PICU.

**Acknowledgments**

The authors thank PICANet for providing anonymized data on intensive care admissions for children with EV/HPeV infections.

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