

# PEPtalk 3: oral aciclovir is equivalent to varicella zoster immunoglobulin as postexposure prophylaxis against chickenpox in children with cancer – results of a multicentre UK evaluation

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## ABSTRACT

**Objective** To compare the occurrence of chickenpox in children with cancer who received varicella immunoglobulin (VZIG) or aciclovir as postexposure prophylaxis (PEP).

**Design** Prospective multicentre service evaluation of children with cancer who received either VZIG or aciclovir as PEP following significant exposure to varicella zoster virus (VZV) over a 24-month period from May 2018.

**Setting** Data were collected from 9 UK Paediatric Oncology Primary Treatment Centres.

**Patients** Children under 16 years old with a diagnosis of cancer and/or previous haematopoietic stem cell transplant who were VZV seronegative at exposure and/or diagnosis and received PEP following significant VZV exposure.

**Main outcome measures** The primary outcome was the incidence of breakthrough varicella within 6 weeks of VZV exposure and treatment with PEP.

**Results** A total of 105 eligible patients were registered with a median age of 4.9 years (range 1.1–10.5 years). Underlying diagnoses were acute leukaemia (64), solid tumours (22), Langerhans cell histiocytosis (9), central nervous system (CNS) tumours (8) and other (2). Aciclovir was received by 86 patients (81.9%), 18 received VZIG (17.1%) and 1 valaciclovir (0.9%). There were seven reported break-through VZV infections in 103 patients at follow-up (7/103, 6.8%). Clinical VZV developed in 5/84 of the aciclovir group (6.0%, 95% CI 2.0 to 13.3) and 2/18 of VZIG group (11.1%, 95% CI 1.4 to 34.7). All breakthrough infections were either mild (5/7) or moderate (2/7) in severity.

**Conclusion** Aciclovir is a safe and effective alternative to VZIG as VZV PEP in children with cancer and should be considered as standard of care.

## INTRODUCTION

Varicella zoster virus (VZV) is the cause of chickenpox, a ubiquitous and highly contagious childhood illness which, in the majority, follows a benign clinical course with subsequent immunity.<sup>1,2</sup> However, for immunocompromised children, primary VZV infection can cause severe disseminated disease, requiring hospital admissions and interruption to cancer treatment and rarely, death.<sup>3–10</sup>

Approximately, a quarter of the 1500 children diagnosed with cancer in the UK annually do not

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Varicella zoster virus (VZV) can cause morbidity and treatment delays for children with cancer in the UK.
- ⇒ Practice varies in the choice of postexposure prophylaxis after exposure to VZV between varicella zoster immunoglobulin (VZIG) and oral aciclovir.

## WHAT THIS STUDY ADDS

- ⇒ A national shortage of VZIG in August 2018 led to a recommendation for oral aciclovir to be used as postexposure prophylaxis (PEP).
- ⇒ Oral aciclovir is a safe and effective alternative to VZIG for VZV postexposure prophylaxis for children with cancer.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ There are strong economic arguments to favour the use of oral aciclovir as a significantly cheaper alternative to intramuscular VZIG, especially as supplies of VZIG remain scarce. The use of aciclovir as an effective agent for PEP could be applied to other patient groups in addition to children with cancer.

have immunity to VZV.<sup>11</sup> By the nature of their disease and its treatment, they are at high risk of severe infection following exposure to VZV. Furthermore, immunity at cancer diagnosis may not confer adequate protection to subsequent exposure, as both malignancy and chemotherapy impair the body's ability to produce and maintain an antibody response.<sup>12–15</sup> Studies suggest 17%–35% of their cohorts lost immunity to VZV in the period of time after cancer diagnosis and cases of chickenpox developing in those who were seropositive at diagnosis have been described.<sup>12–15</sup> This phenomenon is reflected by the difference in risk assessment described in Public Health England (PHE) guidance, published in 2017, differentiating immunocompromised patients into those who can maintain immunity and mount a response on exposure to VZV (Group A) and those who may have lost immunity or the ability to produce a



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sufficiently protective response through their disease or treatment (Group B).<sup>16</sup>

The UK does not currently offer routine VZV vaccination on the national childhood immunisation programme. Guidance to minimise exposure, such as vaccination of susceptible household contacts, is inconsistently applied in practice.<sup>11</sup> A French study has shown that up to 38% of cases of significant exposure to VZV in children with cancer are from contacts at school or nursery.<sup>17</sup> Therefore, in countries which do not routinely vaccinate against VZV, such as the UK and France, it is not feasible to prevent high-risk children from exposure.

If exposure to VZV occurs, due to its relatively long latency, there is a window to disrupt viral infection and prevent clinical disease with postexposure prophylaxis (PEP). Following significant exposure, 90% of susceptible individuals develop chickenpox without PEP.<sup>18</sup> Consequently, around 250 cases of exposure requiring PEP are reported annually, according to a survey of paediatric oncology centres.<sup>11</sup> Yet, in the treatment of this significant and frequent issue, the UK's paediatric oncology practice is divided.

Varicella zoster immunoglobulin (VZIG) has until recently been the first-line PEP recommended by PHE and has been demonstrated to reduce and attenuate clinical infection.<sup>4 16 19–21</sup> Its protection is not absolute and it is a costly and scarce resource with the same inherent risks of any blood product.<sup>19 22 23</sup> Following a hiatus in VZIG supply and favourable experience from countries such as Japan where VZIG is not available, oral aciclovir was introduced as an alternative equivalent choice of PEP by a Royal College of Paediatrics and Child Health (RCPCH) Best Practice Statement in 2002.<sup>24 25</sup> However, this is an unlicensed use of aciclovir and historically had not been recommended as the first-line response by PHE due to the lack of formal evidence of comparative effectiveness. In practice, the use of aciclovir as PEP rivals that of VZIG in the UK, with variation among centres regarding aciclovir dosage and duration of treatment.<sup>11 26–28</sup>

The PEPTalk2 study piloted recruitment to a randomised controlled trial to directly compare the effectiveness of aciclovir and VZIG as PEP in children with cancer across several UK centres.<sup>29</sup> Unfortunately, the results of this pilot indicated that it was unlikely to be feasible to recruit sufficient eligible participants to power a full-scale randomised controlled trial. In view of this, an alternative approach was proposed. PEPTalk3 aimed to add to the evidence-base for choice of PEP following exposure to chickenpox in children with cancer through a high-quality service evaluation of outcomes in children that received PEP as part of their routine clinical management, to inform updates to national guidance and appropriately address the risks of varicella in this vulnerable population.

The specific aims of PEPTalk3 were to collect prospective data on children with cancer who were exposed to VZV, the PEP that they received and the rate of breakthrough VZV disease within 6–8 weeks of exposure. The secondary objective of this study was to compare disease severity in children that developed chickenpox despite VZIG or aciclovir.

## METHODS

This was a UK multicentre service evaluation of children with cancer who received either VZIG or aciclovir as PEP following significant exposure to VZV disease over a 24-month period from 1 May 2018.

During the study period, PHE issued guidance that aciclovir should be used as first-line PEP in immunocompromised patients

in the absence of renal impairment or intestinal malabsorption, in response to a national shortage of VZIG in August 2018.<sup>30</sup>

Eligible participants were identified by healthcare professionals at the participating oncology centres and through the receipt of VZIG supply requests. A study proforma was completed to collect data on baseline demographics, cancer diagnosis, current and recent oncology treatment, VZV serostatus if known and type of PEP received (including timing and dose of VZIG or dose/duration of aciclovir). Each patient was followed up for 6–8 weeks following exposure by their local oncology team to identify cases of breakthrough clinical varicella infection. In these cases, information on markers of disease severity were also collected.

## Eligibility

Inclusion criteria were patients under 16 years of age with a diagnosis of cancer and/or having received a haematopoietic stem cell transplant (HSCT), VZV seronegative at the point of exposure or, if not known, VZV seronegative at cancer diagnosis (unless within 12 months of HSCT) and having received PEP following significant exposure to VZV. VZV seronegativity was determined at either the point of exposure, or if this was not available, at the point of diagnosis.

In line with PHE guidance, significant exposure was defined as contact with a case of chickenpox between 48 hours before onset of rash and crusting of lesions or a household exposure or non-household exposure if in the same room for longer than 15 min or face-to-face.

## Sample size

The study was powered to detect large differences of about 20% between groups (80% power, 5% significance) and was designed when it was assumed numbers in each group would be similar at about 50 per group.

## Statistical analysis

The number of cases of breakthrough varicella disease as well as severe disease in each group (VZIG vs aciclovir) was summarised as percentages with 95% CI and compared using a two-sided Fisher's exact test with 5% significance level. The difference between the percentages was also calculated with 95% CI. Logistic regression to adjust for baseline differences of key demographic variables was planned but not done due to small numbers.

## Outcome measures

The primary outcome was the incidence of breakthrough varicella within 6 weeks of VZV exposure and treatment with PEP. Breakthrough varicella infection was defined as a clinical diagnosis of chickenpox with or without diagnostic confirmation (eg, blood/vesicle fluid PCR), necessitating treatment for VZV.

In cases where breakthrough VZV infection occurred, secondary outcomes included clinical severity of chickenpox assessed on D3–5 of illness using a standardised score,<sup>31</sup> level of hospital care and duration of admission, delay in cancer treatment and other morbidity/mortality resulting from VZV infection.

## Ethical considerations

PEPTalk3 was a non-funded, clinician-led service evaluation supported by PHE. This study did not involve any allocation or randomisation of cases to either type of PEP and did not, in any way, influence choice of PEP administered or subsequent management of the child. All data required for this service

evaluation were collected by the healthcare team responsible for the patient's care as part of routine practice following VZV exposure and, if VZV infection developed, treatment of VZV disease. No treatments, samples or investigations additional to routine care were involved. All data were collected anonymously.

St George's University Research Governance team and the PHE Research Support and Governance Office reviewed the protocol and confirmed that this study was a service evaluation and therefore did not require formal ethical approval.

## RESULTS

### Demographic data

A total of 105 eligible patients were registered during the study period from 9 primary treatment centres in the UK. Median age at the time of exposure was 4.9 years (range 1.1–10.5 years). The most frequent diagnosis category was acute leukaemia (n=64, 61.0%). There were two patients (1.9%) who had received haematopoietic stem cell transplants and two patients (1.9%) taking prophylactic aciclovir prior to exposure. Patient characteristics are summarised in [table 1](#).

### VZV serostatus and exposure

Most patients were VZV seronegative at diagnosis (n=89, 84.8%). Serostatus was unknown for seven patients (6.7%), six were equivocal (5.7%) and three were positive (2.8%). At the time of exposure 53 patients were VZV seronegative (50.5%), 51 were unknown/not retested (48.6%) and 1 was equivocal (0.9%). The three patients who were seropositive at diagnosis were all seronegative at exposure.

The majority of VZV exposures were reported to have occurred at school (n=63, 60.0%), followed by the household (n=15, 14.3%) and hospital/clinic (n=15, 14.3%).

### PEP treatment analysis

Of the total eligible patients requiring VZV PEP, 86 were prescribed aciclovir (81.9%), 18 VZIG (17.1%) and 1 valaciclovir (0.9%). All patients receiving VZIG were registered within the first 4 months of the study prior to the national restrictions on VZIG use. Both patients on long-term aciclovir prophylaxis received aciclovir PEP.

Aciclovir was most frequently prescribed 7 days after exposure (n=40, 46.5%) with a range of 0–20 days (median=7 days). The most common dosing regimen used was 10 mg/kg four times a day (n=26, 30.2%); however, there was a notable variation in practice. The course length varied between 5 and 22 days (median=7 days). Most patients prescribed aciclovir and valaciclovir were reported to be compliant (n=85, 97.7%). VZIG was most frequently administered 1 day after exposure (n=7, 38.9%) with a range of 0–8 days (median=1.5). Treatment characteristics are summarised in [table 2](#).

### Post-exposure breakthrough varicella infections

There were a total of 7 breakthrough VZV infections reported in the 103 patients who were followed up after receiving PEP (6.8%, 95% CI 2.8 to 13.5). Median age was 3.8 years (range 2.3–8.0 years). Underlying diagnostic categories were solid tumour (3), acute leukaemia (2) and CNS tumour (2). Rash onset occurred between 8–31 days postexposure (median 20 days).

In the patients who had received aciclovir, 5/84 (6.0%, 95% CI 2.0 to 13.3) developed clinical varicella infection compared with 2/18 (11.1%, 95% CI 1.4 to 34.7) in the VZIG group (difference in proportions for aciclovir vs PEP=–5.2% (95% CI –20.5 to 10.2), exact p=0.60). In the patients who developed

**Table 1** Patient characteristics

	Number of patients (n=105, %)		
	Aciclovir (n=87)	VZIG (n=18)	Total (n=105)
Age (years)			
1<2	3	0	3 (2.9)
2<3	9	3	12 (11.4)
3<4	18	4	22 (20.9)
4<5	18	1	19 (18.1)
5<6	18	4	22 (20.9)
6<7	5	0	5 (4.8)
7<8	8	1	9 (8.6)
8<9	4	2	6 (5.7)
9<10	3	0	3 (2.9)
10<11	1*	3	4 (3.8)
Gender			
Male	60*	9	69 (65.7)
Female	27	9	36 (34.3)
Not known	18		
Diagnosis group			
Acute leukaemia	55*	9	64 (61.0)
CNS tumour	5	3	8 (7.6)
LCH	7	2	9 (8.6)
Solid tumour	18	4	22 (21.0)
Other	2	0	2 (1.9)
VZV serostatus at diagnosis			
Positive	3	0	3 (2.8)
Negative	75*	14	89 (84.8)
Not known	4	3	7 (6.7)
Equivocal	5	1	6 (5.7)
VZV serostatus at exposure			
Negative	39*	14	53 (50.5)
Not known	47	4	51 (48.6)
Equivocal	1	0	1 (0.9)
Source of exposure			
School/nursery	53*	10	63 (60)
Household	12	3	15 (14.3)
Hospital/clinic	12	2	14 (14.3)
Other, for example, party	10	3	13 (12.4)

\*One patient on Valaciclovir.

CNS, central nervous system; LCH, Langerhans cell histiocytosis; VZIG, varicella zoster immunoglobulin; VZV, varicella zoster virus.

breakthrough clinical VZV infection following aciclovir, PEP had been administered from a median of 6 days postexposure (range 0–7 days) for a median duration of 9 days (range 7–13 days). Dosing of aciclovir was the recommended 10 mg/kg four times a day for three of five patients. Both patients in the VZIG group had received an age-appropriate dose on day 1 postexposure.

Breakthrough VZV infections were scored as moderately severe in two of seven cases (one in each of the aciclovir and VZIG groups) and five were of mild severity.

## DISCUSSION

The results from PEPTalk3 are comparable with existing international research supporting aciclovir as an effective alternative to VZIG for VZV PEP treatment in children with cancer. In this study, 5/84 (6.0%) of patients who received aciclovir developed a VZV breakthrough infection compared with 2/18 (11.1%) of those who received VZIG; the upper end of the

**Table 2** Treatment characteristics

	Aciclovir		VZIG	
	Number	%	Number	%
PEP treatment	87*	82.9	18	17.1
Treatment characteristics				
Median timing of PEP treatment initiation	6 days		1.5 days	
Already on treatment	2	2.3	0	0.0
Before 7 days	39	44.8	16	88.9
On Day 7	40	46.0	1	5.6
After 7 days	6	6.9	1	5.6
Median length of treatment	7 days		Single dose	
Breakthrough infection				
Yes	5	5.7	2	11.1
No	82	94.3	16	88.9
Severity of infection				
Mild	4	4.6	1	5.6
Moderate	1	1.1	1	5.6
Severe	0	0.0	0	0.0

PEP, postexposure prophylaxis; VZIG, varicella zoster immunoglobulin.

95%CI for difference in these proportions indicates confidence that aciclovir has no higher than 10% more breakthrough infections than VZIG. The literature suggests VZV breakthrough in 3.1%–13% of patients receiving aciclovir as PEP and 5%–22% of patients receiving VZIG as PEP<sup>10 23 26</sup> However, protocols and practices for their use vary significantly between centres, regions and countries.

Our study has also demonstrated inconsistency in VZV PEP prescribing practice in the UK. While most centres in this study were using aciclovir, there was a notable variation in the timing, duration and dosage prescribed. PHE guidelines from 2019 advise 10 mg/kg (max. 800 mg) four times daily from D7–14 postexposure in children up to 17 years of age.<sup>30</sup> In a study comparing effectiveness of a 7-day course of aciclovir given either immediately post-VZV exposure or starting at day 7 in healthy children, the incidence and severity of VZV infection in the immediate group was significantly higher.<sup>32</sup> This supports updated guidance from PHE to standardise aciclovir VZV PEP dosing at 10 mg/kg four times a day from days 7–14 postexposure in susceptible immunocompromised children aged 4 weeks to 17 years (maximum dose 800 mg four times a day).<sup>33</sup> This may require patients on long-term prophylactic aciclovir to temporarily increase their dose in line with the above.

There was also notable variation in the VZV serostatus assessment practices between participating centres with regard to repeat testing at exposure. Current PHE guidance recommends that all immunosuppressed patients with a history of chickenpox or previous VZV antibody positivity should have immunity rechecked urgently at exposure to advise the need for PEP and to minimise any delay if required. Individuals with VZV IgG <150 mIU/ml in a quantitative assay or negative or equivocal in a qualitative assay should be offered PEP.<sup>33</sup>

The primary source of VZV exposure in our patient cohort was school or nursery (n=63, 60%). Costa *et al* reported that 38% of 52 reported VZV exposure episodes in their French cohort of children with cancer occurred at nursery or school.<sup>17</sup> While vaccination of household contacts of immunocompromised children is recommended, countries such as the UK and France do not include varicella vaccination on their routine childhood immunisation schedules. Hence, it is not currently feasible to

effectively minimise VZV exposure for high-risk children in the community through herd immunity and having readily accessible and effective PEP is therefore essential.

Aciclovir is approximately 50 times less expensive than the equivalent dose of VZIG and does not have the supply constraints that come from using blood products. VZIG also has a small risk of complications as per transfusion of any blood product, for example, transfusion reaction.<sup>34</sup> The administration of VZIG via intramuscular injection can also be unpleasant for children and could pose a risk if the patient is thrombocytopenic as a result of chemotherapy. In the context of a growing evidence base, aciclovir has the potential to be a safe and cost-effective alternative.

This study was limited by the imbalance between the numbers of patients receiving aciclovir and VZIG. Of the 105 eligible patients registered, 86 (81.9%) were prescribed aciclovir. This is likely secondary to the UK severe national shortage of VZIG in June 2018, which led to the review and amendment of the VZV PEP guidelines by PHE. All patients who received VZIG were registered within the first 4 months of the study which would support this further. It was therefore not possible to sufficiently power this study to reach statistical significance or identify specific risk factors for breakthrough infection.

A potential source of bias in this evaluation is that 17 centres initially agreed to provide data for the study but only 9 centres did so. It is unclear why this was the case. However, the nine centres that did provide data had a wide geographical spread across Scotland and England and four were previously using VZIG and five were aciclovir centres.

Where unit preference and anecdotal experience have historically motivated choice of PEP, this study provides further evidence to inform clinical decision making and the development of standardised national guidelines.

## CONCLUSION

This study supports the growing international body of evidence that aciclovir is a safe and effective alternative to VZIG for VZV PEP. While this study was unable to provide a statistically significant comparison, it provides further reassurance for the non-inferiority of aciclovir as PEP treatment for children with cancer. Given the additional patient-centred, logistical and economic arguments for its use, we recommend that aciclovir is considered standard of care in this patient cohort.

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