5 years of *Varicella zoster* immunoglobulin (VZIG) use in a regional issuing centre: If prevention is better than a cure, are we using the best strategy in the era of vaccination?

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Background

- VZIG is a hyper-immune globulin of approx. 700iU per adult dose[1]
- Given to passively protect susceptible high risk contacts of Varicella zoster (VZ):
  - Pregnant
  - Immunosuppressed
  - Baby (<7 days old or ongoing special care nursing)

- Aims to prevent or attenuate infection in patients at risk of complicated disease, and to prevent foetal Varicella syndrome
- £350 (~$450) per vial[2] (dose 1-3 vials in children, 4 vials age 12 and over)
- Protects for 21 days, after which further dose may be needed for any re-exposure[3]
- Imported from US to avoid Creutzdfeldt-Jakob disease; stock may decline with childhood VZ vaccination
- Reported 50% failure rate[4]

- Sheffield Virology Department is a UK regional issuing centre to 6 healthcare trusts
- An audit of VZIG use was undertaken to:
  1. Assess compliance with issuing guidance (as per UK Green Book of Vaccination)
  2. Evaluate the circumstances of VZ exposure and consider if more measures can be taken to protect these vulnerable patients.

UK Methods to prevent VZ infection

Current UK guidance[5]:

1. Avoidance of rash by susceptible high-risk individuals
2. Vaccination (Oka vaccine; 2 dose regimen) of susceptible:
   - Healthcare workers
   - Household contacts of susceptible immunosuppressed patients
3. High-risk individuals with significant VZ exposure (>15 minutes face to face or same room) should be assessed by a healthcare worker, tested if immunosuppressed or no history of VZ infection, and receive VZIG within 10 days. Aciclovir is not UK-licenced for attenuation of VZ infection.

Alternative proposals:

1. Target groups:
   - Screen women in 1st pregnancy and vaccinate postnatally
   - Screen and vaccinate women in childcare professions
2. Universal childhood vaccination

Methods

VZIG issues from 01/01/2011 to 31/12/2015 were reviewed retrospectively.
Data was collected from the prescription sheets alongside supporting laboratory results, laboratory tests forms and available clinical notes on a local laboratory software program, and entered into an Access template for analysis.

Results

242 VZIG issues were reviewed. The breakdown of type, source and significant settings of exposure can be seen in table 1. The majority of VZIG issues were to pregnant women (68%), the commonest type of exposure was to chickenpox (95%) and the commonest source of exposure was to a child (84%).

Key audit criteria:

- Information on time to issue was available for 234 cases: 100% were issued within 10 days, with a mean time of 4.6 days.
- 100% were issued for a correct indication

Other important findings:

- There were 3 episodes of exposure on special care baby units where multiple babies were exposed by a child visitor and required VZIG
- 10/34 babies needed VZIG due to maternal VZ around labour
- 19 patients (8%) had previously received VZIG
- There were 8 lab-reported cases of VZ infection within 28 days of VZIG and 1 late case (35 days); all were exposed by a prolonged or household contact
- Only 6 patients were checked for seroconversion in Sheffield:
  - 3 to look for asymptomatic seroconversion (tested >3/12 from VZIG; 2 positive)
  - 2 tested after further VZ exposures (both had seroconverted)
  - 1 tested when presented with chickenpox
- With 8 VZ infections and a maximum of 4 subclinical cases, this gave a VZIG failure rate of just 5%
- A total of 32 exposures were preventable by current UK guidance (vaccination or rash avoidance in a non-household contact)
- 84 pregnant women needed VZIG due to their own child having chickenpox (VZ susceptibility should have been raised previously)

Table 1

Group	N	Type of exposure			Source of exposure				Setting of exposure	
		Chickenpox	Shingles	Unknown	Own child	Any child	Parent	Classmate	Household	Occupational
Pregnant	165	149	9	7	84	134	0	0	102	16: 13 = teachers 2 = nurses 1=hairdresser
Immunosuppressed	43	40	2	1	2	33	2	12	14	1 (patient exposed by nurse)
Age <18	*33*	*31*	*1*	*1*	*0*	*28*	*2*	*12*	*12*	*0*
Age 18/>	*10*	*9*	*1*	*0*	*2*	*5*	*0*	*0*	*2*	*0*
Babies:										
SCBU	21	17	0	4	0	13	3 (Mother)	0	0	0
<7 days old	13	12	0	1	0	3	7 (Mother)	0	9	0
Total	242	218	11	13	86	183	12	12	125	17

Table 2

	1. Avoidance of rash in non-household contact	2 Current vaccine guidance	3. Targeted vaccination (women after 1st pregnancy)	4. Universal childhood vaccination	Preventable by 1 or more of 1-4
Number of VZIG issues	18	15	84	134	193
VZIG expenditure	£22,450	£12,750	£117,600	£215,600	£228,500
Source vaccination cost	Not applicable	£908.40	£5087.04	£11,143.04	£11,203.60
Balance	£22,450	£11,841.60	£112,512.96	£204,456.96	£217,346.40

Cost Analysis

A crude assessment of the amount spent on VZIG balanced against the cost of different prevention methods was undertaken and can be seen in table 2.
A large amount of money is being spent on VZIG for exposures that could be prevented with our current guidance (rash avoidance and current UK vaccine use). Alternative vaccination strategies could potentially save an even greater amount.

Conclusion

This work highlighted our concordance as a regional issuing centre in cases where VZIG is issued, both by indication and timing. This is expected, since the decision to issue VZIG is made by a Medical Virologist, with clear Green Book indications. Importantly, it has shown that many exposures are preventable by current guidance, and we need to work with our colleagues looking after these patients to identify reasons for this. However, most VZ exposures are from children, and many are of unavoidable nature such as household contacts, where exposure occurs before the rash appears. As VZIG provides only short term protection, it may be beneficial to consider other options of VZ prevention, such as vaccination of other groups. As seen above, universal childhood vaccination could prevent the majority of exposures, save a substantial amount of money, and reduce the burden of VZ infection and its complications, including likely reduction in carer absence from work.
An interesting observation was of a substantially lower failure rate of VZIG compared to that previously reported, the reason for which is unclear. However, follow up testing for seroconversion was absent in the majority of cases, and so the number of subclinical infections may be underreported. Regardless of the lower failure rates observed, there are many reasons to consider alternative methods of protection against VZ exposure. Having accepted measles and rubella as vaccine-preventable rash illnesses of the past, it seems logical to now focus on tackling VZ. This data supports the debate for considering wider vaccination use, preventing infection and its many complications in the vaccinee, and also protecting a vulnerable cohort of patients.

References

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