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Intravenous immune globulin impairs anti-bacterial defences of a cyclophosphamide-treated host

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SUMMARY

Since intravenous immune globulin (i.v.IG) could impair the clearance of autologous IgG-coated erythrocytes by the reticuloendothelial system (RES), we speculated that a patient with leucopenia who died of candida septicaemia following high dose i.v.IG may have had an impairment of his RES function. We therefore studied the ability of intact i.v.IG to impair the clearance of both soluble immune complexes and a relatively avirulent strain of *E. coli* from the blood of mice made leucopenic with cyclophosphamide. In the presence of leucopenia, 800 μg/g i.v.IG prolonged the time to clear 50% of the administered IgG anti-dinitrophenyl immune complex ($T_{1/2}$) from 2·7 min to 12 min, impaired the clearance of *E. coli* and lowered the LD_{50} of the strain five-fold. This impaired clearance of soluble complexes and increased mortality (8/67 versus 37/69, $P < 0{\cdot}001$) following bacterial challenge was present for up to 120 and 60 min, respectively, following the administration of i.v.IG. In contrast, no significant impairment in RES function was noted when 200 μg/g i.v.IG was administered to leucopenic mice, or when cyclophosphamide alone was given to mice before challenge with either soluble complexes or bacteria. In addition, no change in LD_{50} was found when mice were pretreated with 800 μg/g i.v.IG alone. These data suggest that high doses of i.v.IG may impair anti-microbial defences of a leucopenic host and thereby convert a relatively avirulent organism into a pathogen.

Keywords intravenous immune globulin cyclophosphamide

INTRODUCTION

The availability of immune globulin for intravenous use (i.v.IG) has permitted the safe administration of large amounts of gamma globulin to patients. Commercial preparations of i.v.IG are now routinely used to maintain immunoglobulin G levels in patients with agammaglobulinaemia (Ochs, 1979; Roifman *et al.*, 1985). These i.v.IG preparations are also used to treat some patients with idiopathic thrombocytopenia purpura (ITP). Since antibody-coated platelets are taken up and destroyed in the spleen of patients with ITP, a possible mechanism for an effect of i.v.IG may be via its suppression of the reticuloendothelial system (RES). This has experimental support from studies measuring a delay in the clearance of IgG-coated autologous erythrocytes following i.v.IG infusion (Imbach *et al.*, 1981; Fehr, Hofmann & Kappeler, 1982; Bussel *et al.*, 1983a).

While evaluating the use of i.v.IG for the prevention of infections in patients with acute haematologic malignancy and concomitant leucopenia, we described a fulminant, fatal case of disseminated candidiasis following i.v.IG infusion (Cross *et al.*, 1984). In this case, the candidal infection was manifest by diffuse, rapidly ecchymotic skin lesions and meningitis, both of which are highly unusual manifestations of this type of infection in patients with haematologic malignancy and neutropenia. In this patient we speculated that i.v.IG may have induced an impairment in the clearance of circulating microbial pathogens, resulting in an overwhelming infection.

To test this hypothesis further, we studied the effect of i.v.IG on the Fc receptor-mediated clearance of immune complexes and on the clearance of *E. coli* in cyclophosphamide-treated mice. We found that in the presence of cyclophosphamide treatment, high doses of i.v.IG impaired the clearance of these immune complexes and bacteria and thereby enhanced the susceptibility of mice to lethal infection with a relatively avirulent organism.

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MATERIALS AND METHODS

Mice

Six- to seven-week-old female ICR mice weighing 20–27 g were obtained from a colony maintained at the Forest Glen Facility, Walter Reed Army Medical Center.

Bacteria

E. coli E739 (O and K non-typable), originally provided by Dr Paul Quie, Minneapolis, MN was maintained in skim milk at −20°C until use. For clearance and virulence studies, the organism was grown to mid-log phase, washed once and resuspended in normal saline to the desired concentration, spectrophotometrically.

Reagents

Cyclophosphamide (Cytoxan, Bristol-Myers Oncology, Syracuse, NY) and i.v.IG (Sandoglobulin, Sandoz, Inc., East Hanover, NJ) were obtained commercially and prepared according to the manufacturers' directions. Purified murine IgG anti-dinitrophenyl was radiolabelled and covalently cross-linked at the antigen-combining site with a bivalent affinity labelling reagent as described (Plotz *et al.*, 1979). The mixture of oligomers was separated by gel filtration chromatography, and those complexes eluting in the void volume (5–7 IgGs per complex) were used for all studies (Rifai *et al.*, 1982).

Clearance studies

Cyclophosphamide (CTX)-treated animals were injected intraperitoneally with 150 μg/g CTX 4 days before challenge with either oligomer or bacteria, followed by a second dose of CTX (75 μg/g) 3 days later. This resulted in a reduction of white blood cell count from a mean of $7{\cdot}0 \times 10^3$ to less than $0{\cdot}5 \times 10^3$ cells/mm³ (with no neutrophils evident in a smear of the blood). Five to 15 min prior to the study, mice were given either a 'high' (800 μg/g) or 'low' dose (200 μg/g) of i.v.IG intravenously. For the *E. coli* clearance studies, groups of two mice were bled sequentially by tail snips and the colony-forming units (CFU) per volume of blood determined. For clearance studies with oligomers, 50 μl of blood were obtained from the retro-orbital plexus and the amount of radioactivity was measured in a gamma spectrometer. The 1 min sample was calculated as zero time. The amount of radioactivity administered was calculated by subtracting the radioactivity remaining in the syringe after injection from the total radioactivity in the syringe initially. Uptake of radioactivity in the liver was monitored by measuring the radioactivity in excised livers.

LD_{50} determinations

Groups of 4–5 mice that had been pre-treated with either CTX or i.v.IG alone, or with combinations of the two, were then injected i.v. with different concentrations of *E. coli*, strain E739. i.v.IG was administered 1–2 min prior to i.v. challenge with bacteria unless otherwise indicated. Mortality was determined at 96 h and LD_{50} calculated by the method of Reed & Muench (1938).

RESULTS

Intravenous injection of i.v.IG resulted in a dose-dependent impairment in the clearance of soluble IgG immune complexes. Approximately 1% of total injected radioactivity was found in the circulation at 1 min (used as time zero) after injection, with little variation from experiment to experiment. Fifty per cent of the radiolabelled oligomer ($T_{1/2}$) was rapidly removed from the circulation of untreated mice (2·25 min, Fig. 1a), or mice treated to the point of leucopenia with CTX (2·75 min, Fig. 1b), respectively. The administration of i.v.IG delayed the clearance

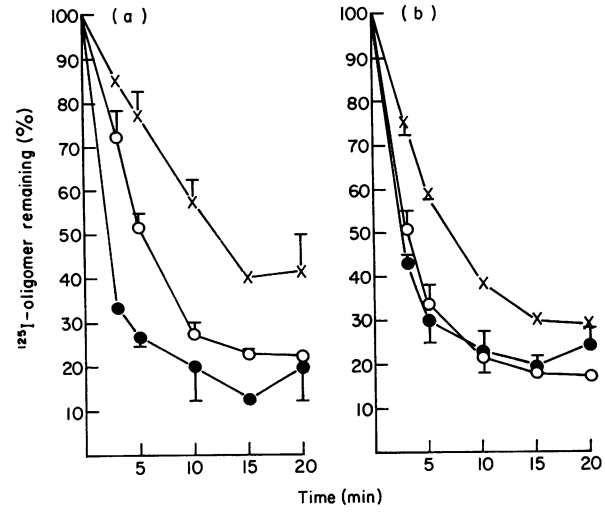

Fig. 1. Clearance of ^{125}I-murine IgG anti-dinitrophenyl immune complexes in mice: with no pre-treatment with cyclophosphamide (a), and with cyclophosphamide pre-treatment (b). Data points represent mean ± s.d. of at least three mice. In the absence of error bars, data represent clearance by one mouse at that time period. Mice that have not received i.v.IG pre-treatment are shown by solid circles; mice that were pre-treated with i.v.IG at 200 μg/g are shown with open circles and mice that are pre-treated with i.v.IG at 800 μg/g are depicted by ×. $T_{1/2}$ values were as follows: no pre-treatment, 2·25 and 2·75 min (a, b respectively); i.v.IG 200 μg/g, 5·25 and 3·25 min (a, b respectively): i.v.Ig 800 μg/g, 12 and 6·5 min (a, b respectively).

of radiolabelled oligomer in a dose-dependent manner in mice that did not receive cyclophosphamide (Fig. 1a). However, in mice that did receive cyclophosphamide, there was a delay in clearance only in mice that received the 800 μg/g dose of i.v.IG (Fig. 1b).

Whereas i.v.IG delayed the clearance of bacteria from the blood of CTX-treated mice, in contrast, it improved bacterial clearance in non-CTX-treated mice. There was no difference between colony-forming units per ml (CFU/ml) at 1 min, 2 h or 24 h when CTX-treated mice were compared to normal mice (Fig. 2a) without i.v.IG infusion. Low dose i.v.IG (200 μg/g) improved the clearance of the bacteria in the non-CTX-treated mice but not in the CTX-treated mice (Fig. 2b). High dose i.v.IG, however, markedly impaired the clearance of the *E. coli* strain in the CTX-treated mice (Fig. 2c). The CFU/ml in the blood at 24 h were approximately one log higher in this group than in any other group. Bacterial clearance was again improved in the non-CTX-treated mice.

When mice were treated with both CTX and i.v.IG there was an increased mortality when compared to mice pre-treated with either i.v.IG or CTX alone (Table 1). When challenged with 1×10^6–2×10^7 CFU of *E. coli* E739, groups of mice given CTX alone or CTX plus low dose i.v.IG had the same mortality (12%). The addition of 800 μg/g i.v.IG to CTX increased the mortality more than four-fold (to 54%, $P < 0{\cdot}001$ compared to CTX treatment alone). There was no mortality in the group of mice given only high dose i.v.IG prior to challenge with E739. The data, which represent the sum of seven separate experiments, were highly consistent from experiment-to-experiment.

The enhanced susceptibility of mice to lethal infection with the *E. coli* test strain was also reflected by a change in LD_{50}

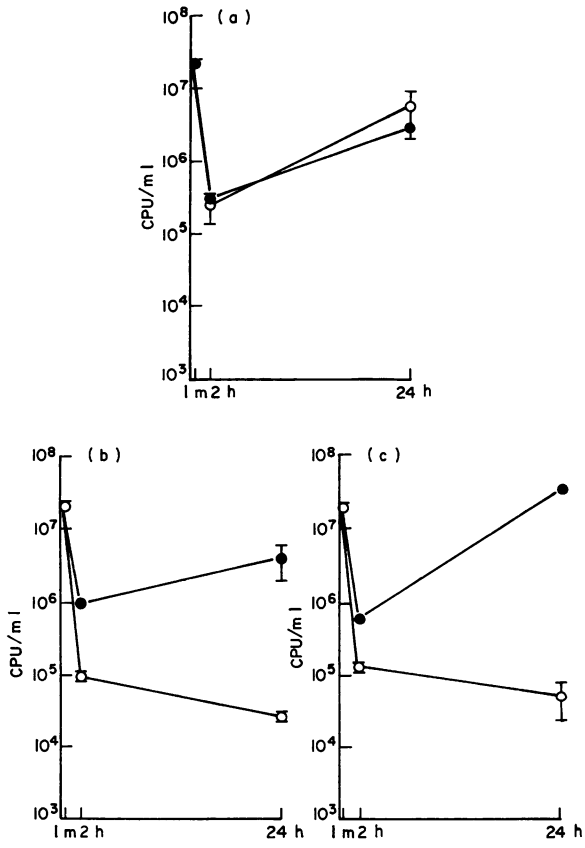

Fig. 2. Clearance of *E. coli*, strain 739 in mice: with no pre-treatment with i.v.IG (a), pre-treatment with i.v.IG, 200 μg/g (b), and with i.v.IG, 800 μg/g (c). Data points represent mean ± s.d. of at least three mice. In the absence of error bars, data represent clearance by one mouse at that time point. Cyclophosphamide-treated mice are shown by solid circles; mice that have not been treated with cyclophosphamide are depicted by open circles.

(Table 1). As previously noted (Ziegler, 1988) there is a fairly sharp change in the LD_{50} of Gram-negative bacilli performed in mice over a narrow range of bacterial inocula. The LD_{50} of strain E739 for untreated mice was $3{\cdot}4 \times 10^8$ CFU. CTX pre-treatment lowered the LD_{50} forty-fold to $8{\cdot}2 \times 10^6$ CFU, and the addition of low dose i.v.IG resulted in an LD_{50} of $4{\cdot}4 \times 10^6$ CFU. High dose i.v.IG reduced the LD_{50} to $1{\cdot}6 \times 10^6$ CFU, a greater than five-fold increase in the susceptibility to infection and death compared to CTX pre-treated mice. These results are consistent with a stepwise increase in susceptibility to lethal infection of mice by this relatively avirulent *E. coli* as reflected by the observed decrease in LD_{50}. This progression of enhanced susceptibility continued as the dose of i.v.IG administered increased.

Since the delay in clearance of the oligomers was observed when the high dose i.v.IG was injected 15 min before the administration of the oligomers, we examined the time dependency of this phenomenon. In the absence of i.v.IG, CTX-treated mice rapidly cleared the oligomer ($T_{1/2}$ was 3 min, Fig. 3). A delay in the clearance was observed when the oligomer was given as early as 1 min after the i.v.IG ($T_{1/2}$, 10 min), was most prolonged when oligomer was given 10 min after i.v.IG ($T_{1/2}$, 35 min) and was still evident when oligomer was administered 60

Table 1. Mouse mortality after challenge with *E. coli*.

Treatment				
	i.v.IG†			
Cyclophosphamide*	800 μg/g	200 μg/g	Mortality‡	LD_{50}§
−	+	−	0/15 (0)	$3{\cdot}4 \times 10^8$
+	−	−	8/67 (12)	$8{\cdot}2 \times 10^6$
+	−	+	2/17 (12)	$4{\cdot}4 \times 10^6$
+	+	−	37/69 (54)	$1{\cdot}6 \times 10^6$

* Initial dose 150 μg/g followed in 3 days by 50 μg/g. Bacterial challenge was given 1 day after second dose of cyclophosphamide.

† Administered as a single dose intravenously 1–2 min before bacterial challenge in a volume of 0·20–0·33 ml.

‡ Mice challenged with 1×10^6–2×10^7 CFU of E739. Results are expressed as number of mice dead/total in group with percentage mortality given in parentheses. Data represent the sum of results of seven separate experiments. The difference between cyclophosphamide alone and cyclophosphamide and 800 μg/g i.v.IG was significant at $P < 0{\cdot}001$ level (Chi-square test, one-tailed). Differences between cyclophosphamide alone and other groups were not significant.

§ LD_{50} in colony forming units (CFU). LD_{50} was determined with groups of five mice. Groups received 1×10^6, 5×10^6, 1×10^7, 5×10^7, or 1×10^8 CFU. Mortality was determined at 96 h. Data represent one determination. Each LD_{50} determination was repeated at least a second time with less than a two-fold difference between determinations.

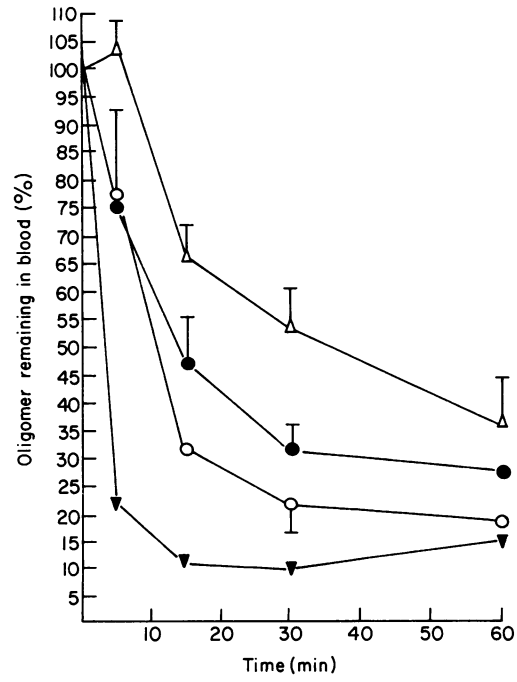

Fig. 3. Clearance of ^{125}I-murine IgG anti-dinitrophenyl immune complexes by mice pre-treated with cyclophosphamide and by i.v.IG, 800 μg/g, given at different times before administration of oligomers: 1 min, (○); 10 min, (△); 120 min (●). The clearance of oligomer by mice given cyclophosphamide but no i.v.IG is shown by (▼).

min after i.v.IG ($T_{1/2}$, 8·5 min, data not shown) and even at 120 min ($T_{1/2}$, 14 min).

When the *E. coli* was administered to CTX-treated mice at an inoculum below the LD_{50} ($9{\cdot}3 \times 10^6$ CFU), 18% (2/11) of mice died in the group that did not receive high-dose i.v.IG (data not shown). When the same inoculum was administered intravenously 1 min following i.v.IG, 60% of mice died (6/10) and the CFU/ml in the blood at 24 h was 840 times that observed in the group that did not receive i.v.IG. An increased mortality (45%, 5/11) was still observed when bacteria were given 60 min following the i.v.IG. In summary, a delay in the clearance of oligomer and an excess mortality varied with the time interval between i.v.IG administration and mouse challenge. But in both assays, an effect attributable to the high dose i.v.IG was observed as long as 60 min following the administration of i.v.IG. In the case of the *E. coli* challenge, the group having the highest mortality also had the highest count of circulating bacteria at 24 h following infection.

DISCUSSION

Our data show that the administration of high doses of i.v.IG to mice resulted in a delay in the clearance of immune complexes, both in the presence and absence of cyclophosphamide-induced changes in the reticulo-endothelial system (Fig. 1a & b). As in the clinical situation, we followed the effect of cyclophosphamide on the reticulo-endothelial system by following changes in the neutrophil count. The administration of i.v.IG to non-leucopenic mice promoted the clearance of *E. coli* from the blood (Fig. 2b and c vs a, open circles); however, this bacterial clearance-enhancing effect of i.v.IG was not seen when the mice were rendered leucopenic (Fig. 2b, c solid circles vs open circles). In addition, neutropenic mice that were pretreated with i.v.IG were killed by less *E. coli* (i.e., had a lower LD_{50}) than were leucopenic mice that did not receive i.v.IG. Thus pretreatment of mice with i.v.IG enhanced the susceptibility of mice to lethal infection with a relatively avirulent organism. These data imply that under certain conditions, the administration of i.v.IG may actually impair rather than enhance host anti-microbial defences.

The development of gamma globulin in preparations safe for intravenous use has permitted the administration of larger amounts of this product than was possible with the intramuscular preparations. This has facilitated the treatment of patients with hypo-gammaglobulinaemia, which was the original indication for the use of i.v.IG. Since the introduction of i.v.IG, however, its use has been widened to include treatment of patients with idiopathic thrombocytopenia purpura (ITP) (Imbach *et al.*, 1981; Fehr, Hofmann & Kappeler, 1982; Bussel *et al.*, 1983a), myasthenia gravis (Arsura *et al.*, 1986), multiple sclerosis (Schuller & Govaerts, 1983), autoimmune neutropenia of infancy (Bussel *et al.*, 1983b), red cell aplasia (Clauvel *et al.*, 1983), Kawasaki disease (Chavenet *et al.*, 1985) and bacterial sepsis (Von Muralt & Sidiropolis, 1981; Christensen *et al.*, 1984; Gonzalez *et al.*, 1985). Whereas the replacement of gamma globulin in patients with hypogammaglobulinaemia requires a dose of i.v.IG of 200 mg/kg once every 3–4 weeks, much higher doses of i.v.IG given more frequently have been utilized in these latter situations. For example, in the case of ITP, 800 mg/kg/day for 5 consecutive days is a common regimen. This is accompanied in many cases by a delay in the clearance of radiolabelled, IgG-coated erythrocytes in these patients. Whether the demonstrable delay in clearance is the mechanism by which i.v.IG confers its beneficial effect in ITP is still not clear.

The results of the present studies suggest that a preparation of monomeric gamma globulin at high enough doses can induce a state of blockade of Fc receptors in the liver and impair clearance of soluble immune complexes. Since the preparation of i.v.IG used in these studies has an intact Fc portion of the molecule, occupancy of Fc receptors is one possible mechanism for the blockade. In support of this is the finding that injection of this preparation was shown to delay the clearance of radiolabelled IgG-coated erythrocytes in man (Imbach *et al.*, 1981; Fehr, Hofmann & Kappeler, 1982; Bussel *et al.*, 1983a) presumably via an Fc receptor-mediated mechanism. This delay in clearance of IgG-coated erythrocytes is also strong evidence for a temporary reduction in the capacity of Kuppfer cells and splenic macrophages of the RES to take up immune complexes via Fc receptors. Although temporary blockade of Fc receptor function has been documented using aggregates of IgG (Finbloom & Plotz, 1979), this study documents that a non-aggregated preparation of IgG may have similar effects. Although treatment of mice with CTX resulted in a partial reversal of the blockage induced by i.v.IG, the mechanism underlying this was unclear. Whether the induction of blockade by aggregates is similar to monomers is unclear, especially in light of some recent data which suggest monomeric IgG may bind to the Fc receptor but not be internalized (Jones, Nusbacher & Anderson, 1985) whereas a soluble immune complex will bind to the Fc receptor and both Fc receptor and immune complex will be destroyed by the cell. Indeed, a recent study presented data that supported the concept that serum (monomeric) IgG competes with the immune complexed IgG for Fc receptors *in vivo*, and suggested that the concentration of serum IgG is a major determinant of Fc-dependent RES function (Kelton *et al.*, 1985). In addition to a specific blockade of Fc receptor function, the RES may be non-specifically suppressed by large doses of i.v.IG, especially in the presence of neutropenia.

Earlier reports by Derby & Rogers (1961) demonstrated that the clearance of *S. aureus* from the bloodstream of rabbits was unaffected by either induced neutropenia or thorotrast-induced reticuloendothelial (RE) blockade alone; however, in the presence of both induced neutropenia and RE blockade, there was a profound delay in the clearance of *S. aureus*. We now show a similar effect with *E. coli* following high doses of i.v.IG. Our present study raises the possibility that the combination of i.v.IG-induced Fc receptor blockade and simultaneous cyclophosphamide-induced changes of the RE system in a patient with a bacteraemia may result in overwhelming infection. While many patients who receive cyclophosphamide undoubtedly have received i.v.IG without any such adverse effects, the presence of certain situations such as an ongoing septic episode, may be necessary for such an event to occur during the infusion of i.v.IG. Indeed, others have reported that neutropenic patients may become septic following the infusin of i.v.IG (Kekomaki *et al.*, 1984). In an experimental model of infection with *H. influenzae* b, i.v.IG treatment results in a higher early mortality than did treatment of controls with saline. Moreover, the combination of antibiotics and i.v.IG was less efficacious than antibiotics alone (Schreiber *et al.*, 1987).

There are other mechanisms whereby gamma globulins may

reduce host defences. Immunoglobulin has been shown to affect immunocompetent cells both *in vivo* and *in vitro* and thus affect host defences. Human immunoglobulin paraproteins from patients with multiple myeloma compromise the chemotactic, chemiluminescent and bactericidal ability of human neutrophils *in vitro* (Van Epps, Reed & Williams, 1978; Van Epps & Brown, 1981). In addition, passively administered antibody can impair the ability of an animal to mount an antibody response upon subsequent exposure to an antigen (La Via & La Via, 1978). This may occur by multiple mechanisms (Haughton, 1974; Newland *et al.*, 1983). It has recently been suggested that high doses of i.v.IG may affect the course of infection with cytomegalovirus through its effect on NK cells (Engelhard *et al.*, 1986). Thus it might be expected that the infusion of pharmacologic amounts of i.v.IG may modulate host immune responses.

The administration of i.v.IG has been beneficial to patients with hypogammaglobulinaemia when the product is given at physiological replacement dosages and to many patients with ITP when given at pharmacologic doses. Two lines of evidence, however, suggest a cautious application of this therapy to other diseases: (1) the experimental data on the possible adverse effects of passively administered antibody on both host antibody response and neutrophil function and (2) the demonstration of impaired clearance by the RE system in man following high doses of i.v.IG. There is also a relative paucity of data on the effects of pharmacologic amounts of i.v.IG given to man under different clinical conditions. It may be that in high doses or in specific clinical situations such as cyclophosphamide therapy i.v.IG may present certain adverse effects as is the case with anti-microbial chemotherapeutic agents. The demonstration of this study that pharmacologic amounts of i.v.IG may actually impair host defences in one well-defined situation reinforces this need for caution. There may be an upper limit to the amount of i.v.IG that may be given before one encounters adverse effects. Thus, should it eventually be demonstrated that i.v.IG may be useful either in the treatment or prophylaxis of infection, there may be a strong rationale to develop products that are hyperimmune to specific antigens.

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