表Ⅵ・B-4　照射赤血球M・A・P「日赤」の含有成分の経時的変化
(400ml採血由来，採血後2日目に照射)

2日目	照射直後	7日目	14日目	21日目
照射なしの場合の上清カリウム(mEq/l)	3.8±0.3(照射直後)	32.1±2.1	48.8±2.5	58.6±2.7
照射した場合の上清カリウム(mEq/l)	4.1±0.4	16.7±1.1	21.7±1.5	27.9±1.7
pH	6.4±2.2	6.76±0.03	6.69±0.03	6.67±0.04
2,3-DPG (μmol/gHb)	6.80±0.03	0.5±0.2	0.3±0.1	0.4±0.1

(厚生労働省[1]；P68より改変)

など）や，輸血ポンプを使用すると，短時間内に大量輸血が可能となり高カリウム血症が起こる可能性がある[8]．1.2ml/kg/分以上の輸血速度では高カリウム血症が起こりうる．代謝性アシドーシスや呼吸性アシドーシスなど細胞内からのカリウムの細胞外移行を助長するような因子があると，高カリウム血症が起こりやすくなる．また，新生児や，腎機能低下患者でカリウム排泄が障害されている場合にはとくに注意を要する．

高度の高カリウム血症は心停止の原因となる．

③ **低カルシウム血症**：赤血球濃厚液の保存液には，カルシウムイオンをキレート化して取り除くためにクエン酸が含まれている．また，新鮮凍結血漿にもクエン酸が含まれている．そのため，赤血球濃厚液や新鮮凍結血漿の急速投与により大量のクエン酸が循環血液のなかに入るために，低カルシウム血症が起こりうる．そのために，低血圧，さらには心停止も起こりうる．

④ **代謝性アシドーシス**：赤血球濃厚液の保存中には，血球の代謝により有機酸が産生される．急速大量輸血を行った場合には，それらの酸により代謝性アシドーシスが起こる可能性がある．アシドーシスと低体温は出血傾向を助長する可能性がある[9]．

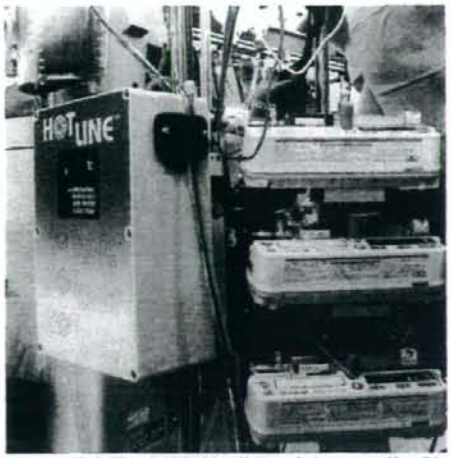
⑤ **代謝性アルカローシス**：クエン酸が代謝されることにより重炭酸ができ，代謝性アルカローシスとなる．

⑥ **希釈性凝固障害**：前述したとおり，循環血液量を超えるような出血に対して輸液やMAP加赤血球濃厚液の投与のみを行った場合には，希釈性凝固障害が起きうる．

⑦ **希釈性血小板減少症**：前述したとおり，循環血液量を超えるような出血に対して，輸液やMAP加赤血球濃厚液の投与のみを行った場合には，希釈性凝固障害が起きうる．

⑧ **低体温**：血小板濃厚液は室温保存であるが，赤血球濃厚液は2～6℃程度で保存されている．新鮮凍結血漿も融解後の温度も低い場合が多い．したがって，血液製剤を急速投与すると，低体温が起こりうる．低体温は血小板機能抑制や血管反応性低下を起こして出血傾向を助長し，出血量を増加させる[10]．輸液・輸血加温器を用いて輸血を行う必要がある．最近は，ホットライン®やレンジャー®など加温効率のよい輸液・輸血加温器が市販されている（**図Ⅵ・D-3**）．

⑨ **肺機能異常—輸血関連急性肺障害**：輸血関連急性肺障害 transfusion-related acute lung injury（TRALI）は，最近注目されるようになった輸血合併症である．頻度は高くない（0.1%未満）が，死亡にいたる重症例（死亡率は5～20%）も存在する．輸血後6時間以内に発症する．寒気，発熱，呼吸困難，喀痰を伴わない咳，低血圧，低酸素血症などが起こる．胸部エックス線の写真上では，多数の結節と下肺野に浸潤影を認め，心拡大や肺血管陰影の



(厚生労働省編：血液製剤の使用にあたって，第3版，じほう社，2005，p.40)[1]

図Ⅵ・B-3　出血に伴う血液成分の変化と輸液・輸血製剤の基本

増強がないことなどが特徴的である．これらの症状は48時間から96時間以内に改善・消失する．全血製剤や，新鮮凍結血漿，血小板濃厚液など高力価の白血球抗体を含む血液製剤の使用で起こりやすい．ただし，MAP加赤血球濃厚液で起きた例も報告されている．

⑩ **酸素解離曲線のシフト**：輸血用血液はその保存中に2,3-ホスホグリセリン酸（DPG）が枯渇する．その結果，酸素解離曲線の左方シフトが起こる．そのため，Hbは組織で酸素を放出しにくくなる．輸血を行っても，組織酸素化の改善が起こるまでには2,3-DPGレベルが回復するまで数時間がかかるといわれている．しかし，最近の報告では，輸血により比較的速やかに組織酸素化が改善することが示唆されている[11]．

⑪ **ナトリウム負荷**：新鮮凍結血漿1単位には0.8g程度のNaClが含まれる．新鮮凍結血漿の大量投与によりナトリウム負荷が起こりうる．代謝性アシドーシスの治療に，炭酸水素ナトリウムを大量に投与した場合にも高ナトリウム血症が起こる．

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(稲田英一)

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Letter to the Editors-in-Chief

Pitavastatin attenuates the upregulation of tissue factor in restraint-stressed mice

To the Editor:

Hypercoagulability and thrombotic tendency are frequently induced by a variety of stressors. Indeed, the presence of psychosocial stressors has been associated with increased risk of acute myocardial infarction [1]. The restraint stress model often has been used to investigate the stress response experimentally in terms of pharmacologic, physiologic, or pathologic phenomena in vivo [2]. Tissue factor (TF) is a key procoagulant gene because it is the primary cellular initiator of the coagulation protease cascade and serves as a specific cofactor for plasma factors VII/VIIa [3]. We previously reported that a restraint (immobilization) stress, a typical physicopsychological stress, to mice induced the TF gene expression in several tissues, including kidneys and adipose tissues [4]. Statins, 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, have been broadly used for the prevention from cardiovascular diseases primarily with their lowering serum cholesterol levels. Statins also exert pleiotropic and beneficial effects on coagulation system, which are regarded to be independent of cholesterol lowering action. In particular, statins have been shown to reduce the TF expression in lipopolysaccharide-stimulated macrophages and smooth muscle cells in vitro, and in carotid lesions of cholesterol-fed rabbits in vivo [5,6].

We have observed that pitavastatin attenuated the upregulation of TF gene in restraint-stressed mice. Eight-week-old male C57BL/6J mice were administrated with 10 mg/kg/day of pitavastatin or atorvastatin for 3 weeks before the animals received restraint stress. Restraint stress, RNA extraction and RT-PCR assay were performed, as described previously [4]. All procedures were carried out according to the protocol approved by the Animal Care and Use Committee of Nagoya University. Twenty hours of restraint stress to mice caused a substantial induction of TF mRNA in the kidney and adipose tissues [4], which has been regarded to be a major source of TF [7]. Pitavastatin attenuated the induction of TF mRNA by stress in these tissues in about 50% of the control (i.e., statin free) mice, while atorvastatin did not (Fig. 1). As plasma cholesterol levels were not affected by statins in these mice (not shown), pitavastatin could suppress the upregulation of TF gene independently of cholesterol lowering action in restraint-stressed

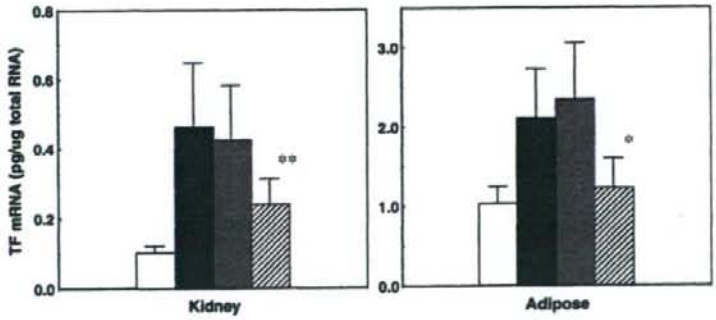

Figure 1 Eight-week-old mice had been administered with pitavastatin (10 mg/kg/day) or atorvastatin (10 mg/kg/day) for 3 weeks ($n=6$, respectively), followed by 20-h restraint stress. As a control group, we prepared non-stressed mice and 20-h-stressed mice without statin therapy ($n=6$, respectively). Kidneys and adipose tissues were harvested and analyzed for TF mRNA by quantitative RT-PCR. White bars: no restraint stress; black bars: only 20-h restraint stress; dark gray bars: pre-treatment with atorvastatin followed by 20-h restraint stress; hatched bars: pre-treatment with pitavastatin followed by 20-h restraint stress. $^{*}p<0.05$; $^{**}p<0.04$.

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mice. The inhibition of HMG-CoA reductase by statins leads to the decreased synthesis of cholesterol and its associated precursors, which are isoprenoid products (e.g., geranylgeranylpyrophosphates) from mevalonate. It has also been reported that statins reduces the TF expression by suppressing the formation of a geranylgeranylated proteins required for the proper synthesis of TF [8]. Thus, pitavastatin could attenuate the TF induction in restraint-stressed mice through the inhibition of geranylgeranylated protein synthesis.

Several differences are observed in pleiotropic effects between statins. Although there have been some reports on the inhibitory effect of atorvastatin on the TF expression in vitro or ex vivo [9,10], its suppressive effect in vivo is still controversial [11,12]. Restraint stress induces inflammatory cytokines (e.g., TNF-α) [4] and oxidative stress markers (e.g., 4-hydroxynonenal and 8-hydroxy-2′-deoxyguanosine) [13], both of which could upregulate TF gene expression in vivo [4,14]. In this context, statins inhibit TNF-α-induced nuclear factor κB (NF-κB) activation [15], which stimulates the TF expression, although they differ in their ability to block NF-κB activation [16]. Pitavastatin could strongly suppress the molecular responses against stress insults, which include the induction of cytokine-induced NF-κB and the production of oxidative stress markers in the ischemic model in vivo in comparison with atorvastatin [17]. Taken together, pitavastatin would attenuate the TF expression induced by stress through the inhibition of TNF-α-induced NF-κB activation (i.e., anti-inflammatory) and its anti-oxidative effect. The finding in this study suggests that pitavastatin contributes to the prevention from thrombotic cardiovascular diseases associated with physicopsychological stress although additional studies to elucidate its mechanism are required.

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Review Article

Intravenous Immunoglobulin Therapy for Acquired Coagulation Inhibitors: A Critical Review

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Abstract

Intravenous immunoglobulin (IVIG) therapy has been used for autoimmune diseases and disorders involving autoantibodies, including coagulation inhibitors. In this review, we have evaluated the efficacy and safety of IVIG therapy for acquired coagulation inhibitors, including factor VIII inhibitor, and for acquired von Willebrand syndrome on the basis of 44 reports published between 1965 and 2005. Among 35 patients with factor VIII inhibitor, we estimated the efficacy of IVIG therapy alone (which includes complete remissions and partial responses with a clinical benefit) to be 30% (11 cases), whereas the response to combination therapy with IVIG plus immunosuppressive agents (eg, corticosteroid, cyclophosphamide) seemed to be better (approximately 70%, 33/45 cases) than with IVIG therapy alone. In acquired von Willebrand syndrome, the efficacy of IVIG therapy was estimated to be 30%. The response to IVIG therapy appears to occur rapidly, and coagulation inhibitors seem to be neutralized immediately. Moreover, severe complications or side effects rarely occur during IVIG treatment. IVIG therapy thus may be considered one choice for treating acquired coagulation inhibitors, although its efficacy improves when used in combination with immunosuppressive agents.
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Key words: Intravenous immunoglobulin therapy; Acquired coagulation inhibitors; Autoimmune disease; Factor VIII inhibitor; von Willebrand syndrome

1. Introduction

Intravenous immunoglobulin (IVIG), a highly purified immunoglobulin G (IgG) fraction derived from pooled human plasma, is currently one of the most widely used plasma components in the world [1,2]. It was originally introduced as replacement therapy for patients with primary immunodeficiency disorders. In 1981, Imbach et al reported a serendipitous observation that a high-dose infusion of IVIG (2 g/kg of body weight infused over 5 days) was able to transiently increase the platelet count in children with idiopathic thrombocytopenic purpura (ITP) [3]. With the encouragement of this and other reports on ITP [4], the clinical applications of IVIG have increased markedly over the past 25 years to include many autoimmune diseases. IVIG has been shown to be efficacious in clinical trials for graft-versus-host disease [5], myasthenia gravis [6], Guillain-Barré syndrome [7], Kawasaki disease [8], and chronic inflammatory demyelinating polyneuropathy [9]. It has also been used to treat immune neutropenia and coagulation inhibitors [10-12], but its efficacy and safety have not been firmly established.

Coagulation inhibitors, antibodies against individual clotting factors, interfere with blood coagulation. The most common coagulation inhibitor is factor VIII inhibitor, an antibody against factor VIII that neutralizes the coagulant activity of factor VIII. Factor VIII inhibitor develops in patients with hemophilia A as an alloantibody after replacement therapy or spontaneously as an autoantibody in nonhemophilic patients [13], including postpartum patients and those with autoimmune disease, malignancy, or diabetes [14]. Once developed in such patients, factor VIII inhibitor poses a serious problem for the management of bleeding episodes, because any infused factor VIII will be rapidly neutralized and will not be available to induce hemostasis [15]. Although IVIG therapy has been used as one of the immunotherapies

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for eradicating coagulation inhibitors, such an indication is considered off label [2].

The aim of this review is to examine the efficacy and safety of IVIG therapy in patients with acquired inhibitors against factors VIII, IX, or V, and in patients with acquired von Willebrand disease. Cases with lupus anticoagulant were not included in this review. An electronic search of the Medline/PubMed database from 1965 to 2005 was performed to identify relevant articles. This search yielded 108 citations, 72 of which were considered appropriate and reviewed. The bibliography of each review paper was examined to identify articles that may have been missed by our electronic searches.

2. History

In 1983, Nilsson et al reported an interesting observation [11]. A patient with severe hemophilia B and factor IX inhibitor was treated with extracorporeal protein A–Sepharose adsorption to remove the inhibitor, followed by the administration of factor IX concentrate and cyclophosphamide. This procedure produced a 15-fold increase in factor IX inhibitor on one occasion but did not cause any increase of the inhibitor titer on another occasion, when 5 g of IVIG was also given to the patient to restore the reduced IgG level. The investigators suggested that the administration of IVIG appeared to suppress antibody synthesis in hemophilia B patients with factor IX inhibitor.

Three groups of investigators reported the use of IVIG in the management of factor VIII inhibitors in 1984 [12,16,17]. IVIG therapy combined with vincristine produced a transient disappearance of acquired factor VIII inhibitor along with a slow rise of factor VIII activity in a 13-year-old boy with autoimmune disease [16]. IVIG therapy was ineffective in 2 patients with hemophilia A inhibitor [17]. Sultan et al [12] reported that IVIG therapy (0.4 g/kg body weight per day for 5 days) resulted in the rapid, marked, and prolonged suppression of factor VIII inhibitor in 2 patients with acquired factor VIII antibody (autoantibody) but that it had little or no effect in 2 hemophilic patients with factor VIII antibody (alloantibody). They showed by in vitro experiments that IVIG preparations were able to neutralize the anti–factor VIII activity of the patients' plasma and the IgG fraction of the patients' sera. Many articles were subsequently published on the effect of IVIG on acquired factor VIII inhibitors, as is discussed later.

3. Possible Mechanisms of Action

The rapid rise in the platelet count in ITP following IVIG administration is thought to occur through binding to and blocking Fcγ receptors on macrophages, thereby preventing the removal of antibody-coated platelets by the reticuloendothelial system in the spleen and liver [4]. This mechanism, however, does not appear to explain the effect on coagulation inhibitors.

Several hypotheses on the mechanisms of action of IVIG on factor VIII inhibitor have been put forward. Sultan et al and Kazatchkine and Kaveri postulated that anti-idiotypic antibodies present in IVIG preparations neutralize factor VIII autoantibodies [12,18]. $F(ab')_2$ fragments from IVIG preparations inhibited anti–factor VIII activity in $F(ab')_2$ fragments from the patient's plasma. Anti–factor VIII $F(ab')_2$ fragments were specifically retained on an affinity column of Sepharose-bound $F(ab')_2$ from IVIG, indicating that a direct interaction occurred through the antibody-binding sites of both immunoglobulins [19]. Anti-idiotypes against various autoantibodies were shown to be present in pooled normal human polyspecific immunoglobulin. In addition, IgG prepared from elderly donors and multiparous women was reported to contain a higher frequency of neutralizing antibodies against factor VIII autoantibodies [20]. It is puzzling that such an in vitro antibody-neutralizing effect was not always demonstrated, even though in vivo administration of IVIG produced a marked reduction of the inhibitor titer [21,22].

The fall in inhibitor titer following IVIG therapy without simultaneous immunosuppressive treatment appears to be rapid (within several days) in most cases [12,23,24] but is slow (more than 10 days) in others [22,25]. There must be slow effects of IVIG on autoantibody production. In addition to its direct and immediate action on antibodies, IVIG has been proposed to suppress antibody formation by B-cells, a process mediated through the down-regulation of Fcγ receptors [26]. Furthermore, IVIG may induce T-cell suppressor activity [27]. These observations taken together suggest that IVIG exerts its effect on the inhibitor titer through more than one mode of action.

4. Efficacy

4.1. Factor VIII Inhibitor

We extensively reviewed the international literature published from 1965 to 2005. The typical IVIG dosage used for treating factor VIII inhibitor was 0.4 g/kg per day for 5 consecutive days.

The efficacy criteria (ie, the response to IVIG therapy) were as follows [28]: Complete remission (CR) was defined as the disappearance of the inhibitor, partial response (PR) was defined as a decrease in the inhibitor titer by at least 25% of the baseline value, and failure was defined as other than CR and PR.

In Table 1, we present all of the cases in which the efficacy of IVIG treatment alone was evaluated [12,22-25,28-40]. The response to IVIG therapy alone was failure in 11 cases (31.4%) and PR in 21 cases (60.0%), but with a subsequent clinical benefit in only 8 patients. Finally, 3 patients (8.6%) achieved CR. The efficacy of IVIG therapy alone, which includes CR and PR with a clinical benefit, among these 35 patients was estimated to be 31.4% (11 cases). In most cases of CR or PR, the response to IVIG treatment was rapid, and factor VIII inhibitor seemed to be neutralized immediately.

We summarize the responses to combined therapy with IVIG plus immunosuppressive agents in Table 2 [21,25, 28,32,35,38-52]. The response to IVIG plus steroid and/or cyclophosphamide therapy was better than to IVIG treatment alone. CR was achieved in 19 (73%) of 26 patients who were treated with IVIG plus steroid. In addition, 14 (74%) of 19 patients who received IVIG plus steroid and

Table 1.
Evaluable Patients from the Literature with Acquired Factor VIII Inhibitor Who Were Treated with Intravenous Immunoglobulin (IVIG)*

No.	Reference	Sex/Age, y	Associated Disease	IVIG Dosage, g/kg per d	Inhibitor Titer, Bethesda U		Response	Clinical Outcome
					Before	Nadir (dt†)		
1	Hudak et al [29]	F/40	Postpartum	0.5 × 5 d	16	<1 (105)	CR	Sustained remission
2	Schwartz et al [25]	M/68	CLL	1 × 2 d	1	0 (14)	CR	Sustained remission
3	Schwartz et al [25]	F/83	Diabetes	1 × 2 d	0.9	0 (61)	CR	Sustained remission
4	Sultan et al [12]	M/62	Idiopathic	0.4 × 5 d	25,000	550 (3)	PR	No clinical benefit‡
5	Sultan et al [12]	F/29	Postpartum	0.4 × 5 d	10,500	1000 (3)	PR	No clinical benefit
6	Zimmermann et al [30]	F/64	Idiopathic	0.5 × 8 d	75	10 (25)	PR	Clinical benefit
7	Zimmermann et al [30]	F/70	Idiopathic	0.5 × 8 d	51	3.8 (9)	PR	Clinical benefit
8	Newland et al [22]	F/71	Diabetes	0.4 × 5 d	50	20 (45)	PR	Clinical benefit
9	Heyman et al [31]	M/64	Idiopathic	0.4 × 5 d	47	28 (17)	PR	No clinical benefit
10	Nishida et al [23]	F/39	Idiopathic	0.4 × 5d	115	17 (3)	PR	No clinical benefit
11	Schwerdtfeger et al [32]	F/31	Postpartum	0.5 × 5 d	420	104 (6)	PR	No clinical benefit
12	Sultan et al [33]	M/78	NA	0.4 × 5 d	42	20 (30)	PR	No clinical benefit
13	Sultan et al [33]	M/72	Carcinoma	0.4 × 5 d	38	10 (5)	PR	Transient benefit
14	Schwartz et al [25]	M/54	Alcoholism	1 × 2 d	1228	208 (7)	PR	No clinical benefit
15	Schwartz et al [25]	F/72	Idiopathic	1 × 2 d	880	570 (48)	PR	No clinical benefit
16	Schwartz et al [25]	F/25	Idiopathic	1 × 2 d	280	1.9 (57)	PR	Clinical benefit
17	Schwartz et al [25]	F/38	Postpartum	1 × 2 d	102	56 (22)	PR	Clinical benefit
18	Schwartz et al [25]	M/77	Carcinoma	0.4 × 5 d	39	24 (3)	PR	No clinical benefit
19	Schwartz et al [25]	M/60	Griseofulvin	0.4 × 5 d	29	18 (19)	PR	No clinical benefit
20	Crenier et al [28]	M/65	Cardiomyopathy	0.4 × 5 d	120	72 (30)	PR	No clinical benefit
21	Crenier et al [28]	M/74	Bronchitis	0.4 × 5 d	24	12 (7)	PR	No clinical benefit
22	Michiels et al [24]	F/31	Postpartum	0.5 × 5 d	12	1 (11)	PR	Clinical benefit
23	Lafferty et al [34]	F/42	SLE	0.4 × 5 d	500	185 (NA)	PR	Clinical benefit
24	Walsh et al [35]	F/72	Cholecystitis	30 g × 1 d	6	NA	PR	Clinical benefit
25	Hiller et al [36]	M/57	Surgery	30 g × 5 d	24	20 (2)	F	Transient benefit
26	Casas et al [37]	M/70	Lymphoma	0.4 × 7 d	8.6	35 (NA)	F	Transient benefit
27	Sultan et al [33]	M/45	Vasculitis	0.4 × 5 d	25	28 (NA)	F	NA
28	Pignone et al [38]	F/66	RA	0.4 × 6 d	13	26 (7)	F	NA
29	Hauser et al [39]	F/29	Postpartum	0.4 × 5 d	10	110 (NA)	F	NA
30	Mateo et al [40]	F/82	CLL	0.4 × 5 d	9.5	10 (30)	F	NA
31	Schwartz et al [25]	M/64	Diabetes	1 × 2 d	452	340 (6)	F	No clinical benefit
32	Schwartz et al [25]	F/83	LA	0.4 × 5 d	102	96 (5)	F	No clinical benefit
33	Schwartz et al [25]	F/48	Idiopathic	1 × 2 d	59	46 (2)	F	No clinical benefit
34	Schwartz et al [25]	M/73	Carcinoma	0.4 × 5 d	42	108 (5)	F	No clinical benefit
35	Schwartz et al [25]	M/62	Idiopathic	1 × 2 d	1.4	1.4 (11)	F	No clinical benefit

*CR indicates complete remission; CLL, chronic lymphocytic leukemia; PR, partial response; NA, not available; SLE, systemic lupus erythematosus; F, treatment failure; RA, rheumatoid arthritis; LA, lupus anticoagulant.

†Number of days after starting IVIG treatment.

‡Subjective evaluation by the doctors in charge.

cyclophosphamide reached CR. Only 2 cases of treatment with IVIG plus cyclophosphamide were reported, and these patients achieved CR [52]. Conversely, 18 (75%) of 24 patients treated with steroid plus cyclophosphamide instead of IVIG achieved CR. This degree of efficacy is consistent with the report by Green et al [45]. In these reports, however, the evaluation of efficacy depended on the patients' symptoms (ie, improvement of bleeding tendency), because the disappearance of inhibitors was not followed up.

Thus, the overall efficacy of IVIG therapy alone is almost 30%, whereas that of a combination therapy with IVIG plus steroid and/or cyclophosphamide is approximately 70%.

Recent reports have described patients with acquired factor VIII inhibitors who rapidly responded to immunosuppressive regimens including rituximab, a monoclonal antibody against CD20+ B-cells [53,54]. These data suggest that immunosuppressive therapy using rituximab could become a powerful tool against coagulation inhibitors.

4.2. Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome is a rare bleeding disorder with laboratory findings similar to those of congenital von Willebrand disease. According to an international registry, acquired von Willebrand syndrome is primarily associated with lymphoproliferative diseases, immunologic and cardiovascular disorders, and solid tumors. The prevalence of acquired von Willebrand syndrome in these underlying disorders is still unknown.

IVIG was also effective in stopping bleeding in acquired von Willebrand syndrome [55]. Several groups reported that acquired von Willebrand syndrome associated with systemic lupus erythematosus [56], monoclonal gammopathy [57-60], malignant lymphoma [61], and prostatomegaly [62], and of undefined origin [63,64] responded well to IVIG therapy. Some patients were successfully treated with the combination of IVIG and desmopressin, but the effect was transient

Table 2.
Responses of Patients with Acquired Factor VIII Inhibitor to Immunosuppressive Agents with or without Intravenous Immunoglobulin (IVIG) Therapy

	IVIG + Pr (26 Cases)			IVIG + Pr + Cy (19 Cases)			Pr + Cy (24 cases)		
Reference	CR	PR	F	CR	PR	F	CR	PR	F
Green et al [41]	1								
Carreras et al [21]	1								
Heyman et al [31]			1†						
OiSullivan et al [42]					1				
Pirner et al [43]					1				
Lionett et al [44]	1								
Pignone et al [38]							1		
Green et al [45]							5		5
Hauser et al [39]							1		
Mateo et al [40]	1								
Schwartz et al [25]	1	1							
Crenier et al [28]	1			1					
Lafferty et al [34]					1				
Sohngen et al [46]							2		
Bossi et al [47]	4		1	8		1	3		
Gandini et al [48]	1								
Dykes et al [49]	4	1	2						
Grunewald et al [50]				2			4		
Mazzucconi et al [51]	3	1							
Delgado et al [52]	1			3	1		2		1
Total	19	3	4	14	4	1	18		6

*Pr indicates prednisolone or dexamethasone; Cy, cyclophosphamide; CR, complete remission; PR, partial response; F, treatment failure.
†IVIG dosage: 0.4 g/kg per d for 2 d.

in most cases. According to data from an international registry, the efficacy of IVIG therapy in acquired von Willebrand syndrome was estimated to be 30% (21/63 patients) [65,66]. Of note, however, is that in most cases the efficacy of IVIG was subjectively evaluated (ie, a good response means to stop bleeding) by the doctors in charge. This efficacy is similar to that for treatment with desmopressin (38/119) or with immunosuppressive agents (23/66), but corticosteroids alone were effective in only 19% of patients (12/63).

4.3. Other Coagulation Inhibitors (Factor V or IX Inhibitor)

Patients with inhibitors against factor V or IX are extremely rare. Only one report described acquired factor IX inhibitor developing in a patient with autoimmune polymyositis [67]. Single-agent therapy with IVIG was effective in suppressing inhibitor synthesis and in stopping bleeding. Another report described acquired factor V inhibitor developing in an 82-year-old female patient following abdominal surgery [68]. Nine-day treatment with IVIG (0.4 g/kg per day) was partially effective in suppressing the inhibitor titer and improving the patient's hemorrhagic diathesis.

5. Safety

Adverse reactions to IVIG therapy are usually mild and self-limited: headache, back pain, low-grade fever, myalgia, and chills. The IVIG preparations currently in clinical use are also assumed to carry virtually no risk of transmitting infectious agents. Rarely, however, serious complications can occur. In recent years, thromboembolic complications have occasionally been reported in patients who received IVIG. Stroke, acute myocardial infarction, and deep vein thrombosis were estimated to occur at an incidence of 3% to 5% [69]. Thromboembolism appeared to develop mainly in patients who had other risk factors, such as an advanced age, being bedridden, and a history of thromboembolism. What triggers thromboembolic complications? During 5 courses of treatment with IVIG (24-54 g/day), the plasma IgG concentration was noted to increase 4-fold, and plasma viscosity increased to beyond the normal range [70]. It appears that increased blood viscosity after high-dose IVIG infusion is responsible for thromboembolism. Slow infusion of IVIG (a daily dose of 0.4 g/kg in not less than 8 hours) has been recommended to prevent thromboembolism [71].

Interestingly, our own review of the literature revealed no thromboembolic complications in 80 patients with acquired factor VIII inhibitor who had received IVIG. It is tempting to speculate that the presence of a coagulation inhibitor may counteract thrombosis formation.

6. Discussion

In general, treatments of acquired coagulation inhibitors are divided into 2 approaches: One is to stop the present bleeding events, and the other is to remove inhibitors by immunomodulative therapy. In cases of acute bleeding in patients with factor VIII inhibitors, conventional management consists of human factor VIII concentrate or desmopressin for low inhibitor levels (<5 Bethesda U) and porcine factor VIII or bypass therapy (eg, recombinant activated

factor VII, activated prothrombin complex concentrates) for high inhibitor levels (>5 Besthesda U). On the other hand, immunosuppressive agents (eg, corticosteroid, cyclophosphamide, azathioprine, rituximab) or IVIG has been used to suppress the generation of coagulation inhibitors. Other approaches are plasmapheresis and immunoadsorption using a protein A–Sepharose column to remove coagulation inhibitors, but the indications for these therapies are limited.

Evaluation of the response to one therapeutic modality in the management of coagulation inhibitors is not always easy, for a number of reasons. First, there are only a few inhibitor patients, and thus it is almost impossible to conduct a randomized clinical trial. There have been only a few such trials on acquired coagulation inhibitors [25,45]. This situation influences the evaluation of efficacy because cases of unsuccessful treatment with IVIG may not have been reported, with only successful cases having been evaluated. Second, most patients present with life-threatening bleeding and are treated with several different therapies simultaneously or sequentially. It is difficult, therefore, to assess the outcome of any single modality. Third, it is known that spontaneous fluctuation or disappearance of the inhibitor may occur [72].

As is shown in Table 1, the efficacy of IVIG therapy alone is not very high (ie, 30%). Moreover, the CR rates for combination therapy with IVIG plus glucocorticoid and/or cyclophosphamide (IVIG plus prednisolone/dexamethasone, 73%; IVIG plus prednisolone/dexamethasone and cyclophosphamide, 74%) did not differ from those of immunosuppressive agents without IVIG (prednisolone/dexamethasone plus cyclophosphamide, 75%) (Table 2). However, the clinical benefits of IVIG include a rapid response and fewer adverse effects, which are frequently observed with the chronic administration of glucocorticoid or other immunosuppressive agents. Regarding the use of cyclophosphamide in particular, it is possible for cytotoxicity to induce myelosuppression and secondary malignancy. Thus, IVIG therapy should be considered for acute massive bleeding in patients with acquired coagulation inhibitors because of its faster action. On the other hand, IVIG therapy costs approximately US $10,000 for a 5-day infusion, which is much more costly than other treatments except rituximab. These considerations taken together suggest that the use of IVIG for the management of acquired coagulation inhibitors might be limited, because whether a given treatment is used depends on the balance between cost and benefit.

7. Conclusion

For patients with acquired coagulation inhibitors against factor VIII, the efficacy of IVIG therapy alone was estimated to be 30% in 35 cases. On the other hand, the response to combination therapy with IVIG plus immunosuppressive agents (eg, corticosteroid, cyclophosphamide) seems to be better (ie, 70% in 45 cases) than IVIG as single-agent therapy. IVIG may be considered as one choice of treatment for acquired coagulation inhibitors, especially when a rapid response is required without myelosuppression, but its use alone would be limited because of its lower efficacy and high cost.

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誌上抄読会

大量出血
—大量出血時の凝固障害について—

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司会：麻酔科医が遭遇する術中合併症の中で大量出血は頻度の高いものです．その中で凝固障害はしばしば治療に難渋します．

A：当科では治療困難な凝固障害に対して数年前からフィブリノゲン製剤を投与しています．現在では大量出血時には頻回にCBC，PT，APTT，フィブリノゲンを測定し，必要な製剤を投与することが当たり前のことになっています．

司会：今回の抄読会では大量出血時の凝固障害について調べてみましょう．まず総説を紹介して下さい．

1 Hardy J-F, de Moerloose P, Samama CM, et al: Massive transfusion and coagulopathy: pathophysiology and implidations for clinical management. Can J Anesth 2006; 53: 6: S 40-58

2 Hardy J-F, de Moerloose P, Samama CM: The coagulopathy of massive transfusion. Vox Sang 2005; 89: 123-7

3 Ketchum L, Hess JR, Hiippala S: Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. J Trauma 2006; 60: S 51-8

4 Hellstern P, Haubelt H: Indications for plasma in massive transfusion. Thromb Res 2002; 107: S 19-22

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Journal Club

Massive Bleeding and Coagulopathy

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B：赤血球の補充が血小板の機能を維持する上で重要であることを強調している文献がいくつかあり，凝固因子の補充だけが出血傾向を改善させるわけではないことがわかりました．

C：赤血球の血小板への影響は具体的にはどのようなものですか？

D：赤血球の存在が物理的にサイズの小さい血小板を血流の周辺部へ押しやって，都合よく血管壁に近接して流れるようにするようです．それ以外にも血小板の活性化への影響があるようです．

C：血小板の機能を維持するには赤血球の投与はどのくらいが必要なのでしょうか？

D：動物実験ではHct 35%以上が必要としています．

B：低体温の凝固因子活性に与える影響についても強調されていました．過去の研究から，低体温による凝固障害は復温により速やかに改善するようです．

司会：赤血球の十分な投与，低体温の予防が重要なことがわかりました．

V：輸血計画は検査結果に応じて赤血球濃厚液(PRC)，新鮮凍結血漿(FFP)，フィブリノゲン(Fg)，血小板濃厚液(PC)，凝固因子製剤の順に投与することでよいでしょうか？

D：基本的にはそうです．ただし，検査結果で血小板数が低値だとしても必ずしも凝固障害の原因がそれによるものとは限らず，Fg値を改善しないと血小板を投与しても効果がなかったという報告から，Fg値の改善を優先することを強調しています．

C：Fgは100 mg/dl以下にならないよう補正するということでよいのでしょうか？

D：そのようですね．その場合，Fg製剤かクリオプレシピテートの投与を推奨しています．

C：FFPの投与量についてはいかがですか？

D：FFPについては“十分な投与”としていますが，実際の必要投与量については明らかでありません．

司会：FFPの投与量について検討した文献ではいかがでしょうか？

5 Chowdhury P, Saayman AG, Collins PW, et al: Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004；125：69-73

E：従来の推奨FFP投与量10～15 ml/kgについて検討した文献でした．FFP 12.2 ml/kgで投与された群と高用量投与33.5 ml/kgの群で，FFP投与前後のPT・APTT・各凝固因子を測定しています．推奨FFP投与量では止血に必要な各凝固因子の目標濃度30 IU/dl（Fg 100 mg/dl）を越えておらず，高用量投与では全凝固因子が是正可能でした．ガイドラインの見直しが必要であると結論しています．また，凝固検査だけでは，凝固因子の推定は困難である点も指摘しています．

司会：凝固検査の信頼性についてですが，以前輸血部から，動脈圧カテーテルからの検体は検査データの信頼性に問題があるとして，穿刺による採血の依頼がありました．動脈圧カテーテルからの採血について検討した文献はありますか？

6 Hoste EA, Roels NR, Decruyenaere JM, et al: Significant increase of activated partial thromboplastin time by heparinization of the radial artery catheter flush solution with a closed arterial catheter system. Crit Care Med 2002；30：1030-4

7 Gregersen RA, Underhill SL, Detter JC, et al: Accurate coagulation studies from heparinized radial artery catheters. Heart Lung 1987；16(6 Pt 1)：686-93

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8 Haynes SR, Allardyce W, Cowan B, et al: Accuracy of coagulation studies performed on blood samples obtained from arterial cannulae. Br J Anaesth 1992；69：599-601

F：3つの文献から，検体を採る前の採血が動脈圧カテーテルの死腔の4倍以上であればPT，Fgに関しては影響がないようです．APTTについては5倍以下では信頼性がなく，9倍以上でもAPTTの延長があるとしています．APTTの検査は信頼できないといえます．

A：大量出血時に穿刺による採血を行うことは現実的でないので，当科では従来どおり動脈圧カテーテルから採血を行い，PT，Fgを指標にしていますね．

司会：当科では胸部大動脈置換術で麻酔導入後，アフェレーシスを行って自己血小板液を確保して大量出血に備える試みを行っています．アフェレーシスにより血小板が活性化されるようですが，そのような血小板の活性化と止血能との関連についてはいかがですか？

9 Dijkstra-Tiekstra MJ, Pietersz RN, Huijgens PC: Correlation between the extent of platelet activation in platelet concentrates and in vitro and in vivo parameters. Vox Sang 2004；87：257-63

G：PCの生成過程や保存期間中に血小板の活性化が生じるようです．血小板の活性化の影響を*in vitro*とCABG術後の患者への投与で検討しています．*in vitro*では保存期間が7日までのPCに比べて，8～12日間保存したPCで活性値の増加がみられました．21人の患者に保存期間が7日までのPCを投与しましたが，血小板の活性化の程度と胸腔ドレーンからの出血量に相関はみられませんでした．

司会：Fgやクリオプレシピテートを使用しても，難治性の凝固障害に遭遇することがあります．これらに対してさまざまな製剤が試みられているようです．

O：最近は第Ⅶ因子の使用についての報告が多いですね．

10 Heilmann L, Wild C, Pollow K, et al: Successful treatment of life-threatening bleeding after cesarean section with recombinant activated factor Ⅶ. Clin Appl Thromb Hemost 2006；12：227-9

H：緊急帝王切開後の出血性ショックに対して最終手段として遺伝子組換え活性型第Ⅶ因子製剤(rFⅦa)を90 μg/kg投与したところ，副作用なく投与後20分以内で止血したそうです．この報告では有用性を認めています．

C：rFⅦaはなぜ効くのでしょう？

H：血液凝固カスケードからⅦ因子が活性化されるとX因子の活性化に繋がります．

B：FFP入れずにrFⅦaを投与すればいいのでしょうか？

A：フィブリノゲンもないと駄目ですね．

O：教科書では外因系で生成するトロンビンは少量で，これのみでは十分でありません．トロンビンがフィードバックしてⅨ・Ⅷなどの関与も加わりさらに大量のトロンビンができることも止血に必要なようです．

11 Niemann CU, Behrends M, Hirose R, et al: Recombinant factor Ⅶa reduces transfusion requirements in liver transplant patients with high MELD scores. Transf Med 2006；16：93-100

I：肝移植でrFⅦaの予防的投与が術中の輸血必要量を減少させるようです．対象はrFⅦaを1回投与した症例11例で検討されていて，複数回投与したものは評価対象から除外していまし

た.

F：ということは投与したけど止血できなかった症例があるということですね．そっちのほうが多かったりして…．

12 Bishop CV, Renwick WE, Tatoulis J, et al : Recombinant activated factor VII : treating postoperative hemorrhage in cardiac surgery. Ann Thorac Surg 2006 ; 81 : 875-9

J：これは心臓手術症例で術後大量出血が持続した場合の治療手段として使用していますが，効果的かつ安全であるとしていました．

13 Romagnoli S, Bevilacqua S, Sorbara C, et al : Small-dose recombinant activated factor VII (Novo Seven) in cardiac surgery. Anesth Analg 2006 ; 102 : 1320-6

K：心臓手術後の難治性出血の症例15例で低用量のrFVIIaの効果を検討しています．治療群はrFVIIaを1.2 mg緩徐静注しています．出血量・輸血量・ICU滞在期間・再手術の頻度について治療効果があったようです．2例脳梗塞がありましたが，積極的に薬物との因果関係を疑うものではなかったようです．投与量の多いものでは急性腎不全の発症率が高いとの報告もあり，血栓症のリスクが指摘されています．急性腎不全の原因については触れていませんでした．

I：低用量でも効果があるということでしょうか？

K：過去の研究では投与量は15～180 μg/kgとまちまちです．1.2 mgはアメリカでの最小単位のようです．

C：文献で推奨されている投与開始時期はいつでしょうか？

K：投与時期は研究によってさまざまで確立されたものはないようです．

司会：rF VII aの安全性について検討された研究はありますか？

14 Shao YF, Yang JM, Lee PH, et al : Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy : a multicenter, randomized, double blind, placebo-controlled trial. Am J Surg 2006 ; 191 : 245-9

L：肝硬変患者の肝部分切除術での第VII因子製剤の止血効果と安全性を検討しています．プラセボ76人，rFVIIa投与50 μg/kgの群71人，10 μg/kgの群74人で比較しています．結果は有効性・安全性に関してもプラセボ群に比べて明らかにできなかったようです．

15 Levy JH, Fingerhut A, Porte RJ, et al : Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury : review of safety profile. Transfusion 2006 ; 46 : 919-33

F：rFVIIaの血友病以外での凝固障害に使用した際の血栓症の合併について過去の報告を集めて評価しています．プラセボ群と発生率に差はなく血栓症が起こりやすくなるとはいえないようです．

16 Karkouti K, Yau TM, Beattie WS, et al : Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. Can J Anesth 2006 ; 53 : 802-9

M：心臓手術後の難治性大量出血症例でのrFVIIaの安全性について検討した文献です．投与した114人と投与しなかった541人で，その有害事象の発症率を比較しています．有害事象は，死亡・脳卒中・腎不全・心筋梗塞・中心静脈血栓症に

ついて検討されました．結果は，それらのリスク上昇との関連性はないとしています．また，rFVIIaは早期投与でより治療効果を発揮するようです．

17 Rizoli SB, Boffard KD, Riou B, et al: Recombinant activated factor VII as an adjunctive therapy for bleeding control in severe trauma patients with coagulopathy: subgroup analysis from two randomized trials. Critical Care 2006；10：R178（この文献は報告ごとか？）

N：これは無作為化比較試験です．136人の規模で検討し，rF VII aを投与した場合，PRC・FFP・PCともに輸血量が減少し，血栓症・多臓器不全などの合併症はプラセボと同程度のようでした．

司会：凝固因子製剤以外で止血効果のあるデスモプレッシン（DDAVP）についてはいかがでしょうか？

18 Lethagen S: Desmopressin in mild hemophilia A: limitations, efficacy, and safety. Semin Thromb Haemost 2003；29：101-6

O：血友病AでのDDAVPの効果を検討したものですが，DDAVP投与によりvon Willebrand factor（vWF）やVIII因子の血中濃度を2～6倍増加させるようです．

C：作用機序を教えて下さい．

O：内皮細胞で産生されるvWFのうち95%が分泌され，残りの5%はWeibel-Palade小体と呼ばれる血管内皮細胞内小器官に貯留されています．DDAVPによりWeibel-Palade小体からvWFが放出されることで効果を発揮すると考えられています．投与量は0.3 μg/kg経静脈的投与で止血効果があるようです．ただし，すべての血友病A患者に有効というわけではなく，患者のVIII因子の基礎値に依存しています．

A：大量出血などの凝固障害に対しての記載はありますか？

O：この文献には記載ありませんが，MGH麻酔の手引きにも薬物治療として列記されています．

司会：アプロチニンについてはいかがですか？

A：アプロチニンは好意的な文献が多かった薬物ですが，2006年1月に危険性を指摘する論文がThe New England Journal of Medicineに報告されてから，同年2月にFDAから勧告が出されました．その後の2006年9月21日に行われたFDA公開会議に，Bayer社がアプロチニン投与患者での死亡・腎不全・うっ血性心不全・脳卒中発作リスクが増大しているとのデータを提示しなかったことが問題になっているようですね．

19 Mangano DT, Tudor LC, Diezel C, et al: The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006；354：353-65

H：冠動脈バイパス術を受ける患者4,374人でアプロチニン，アミノカプロン酸，トラネキサム酸の投与群と非投与群を対象に解析しています．アプロチニン以外の2剤はリスクの増加に関連していないが，アプロチニンは透析を要する腎不全リスクは2倍・心筋梗塞や心不全は55%増加・脳卒中発作/脳症は181%増加したという結果となっています．

O：2006年10月の医薬品安全性情報によれば，その後Bayer社から，開発業務受託機関が，CABGを受けた患者67,000件の既存データを調査し，アプロチニンの投与を受けた患者で死亡・腎不全・うっ血性心不全・脳卒中発作のリスクが増大したことが報告されたようです．

F：止まりすぎるのもよくないのでしょうかね．いずれにせよ現在推奨されている製剤の安全性についての報告に注意していくことも必要です

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ね.

司会：今回の抄読会をまとめさせていただきます．輸血計画は採血結果や臨床症状から判断し，PRC・FFP・Fg・PCや凝固因子製剤の順に投与を行うことは変わらないようですね．輸血計画のみでなく，術中の体温管理など全身管理からも止血効果を高めるよう努力し，刻々と状況の変化していく病態に対応していかなければなりません．当院では急速輸液装置など便利な機械もありますが，大量の輸血製剤やカテコラミンなど大量の薬物が使用されて戦場と化す中，ミスのない麻酔管理をするにはマンパワーの問題も含めて大変な労力が必要です．今回の抄読会で今までの輸血療法とその投与量についての再確認と，使用経験のない凝固因子製剤などの知識を持てたということは日々の麻酔管理への一助になったのではないでしょうか．皆さんご協力ありがとうございました．

*　　*　　*

周術期における輸血療法：総論

Perioperative transfusion medicine——Summary of contents

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◎周術期の輸血療法は出血に対するものと考えてよい．なかでも循環血液量を超えるような大量出血では特別な対応が求められる．もとより周術期の出血には，先天的にせよ，後天的にせよ術前に出血性素因であることが明らかな場合と予期せぬ出血をきたす場合があるが，前者は一部の疾患ではその対応は困難なことはあっても，ほとんどは手術前に対応は可能である．しかし，後者の場合の大部分は局所の止血困難であり，その対応はもっぱら局所的止血を貫徹する以外方法はない．循環血液量を超える大量出血や胸部外科領域における動脈瘤によって惹起される凝固障害はその原因が血小板や凝固諸因子の欠乏のためであり，逆に適切な病態の把握さえ行えば血小板やフィブリノゲンなどの凝固因子の十分な補充で対応は可能である．そのためには，止血凝固のメカニズム，検査の意義およびそれを行うタイミング，そして輸血検査の意義とそのタイミングを十分理解することが求められる．

Key word：周術期輸血療法，大量輸血，希釈性凝固障害，タイプアンドスクリーン，フィブリノゲン

安全な輸血療法は，安全な製剤，適切な検査およびそのシステム，そして的確な個人確認などにより保障される．内科的・あるいは待機的輸血療法とは異なり，外傷や周術期，とくに術中の予期せぬ大量出血時に対する輸血には一般的な輸血システムや，検査・供給体制とは別な観点での，病態の把握や，システムの構築が必要である．

術前の検査とその意義

もっとも典型的な観血的処置である手術では，出血をいかに制御するかが重要な問題であり，結果的に以下に述べるような種々の血液製剤が投与されることもまれではない．というものの，すべての手術に輸血が必要ということもない．そこで，どのような手術において輸血を準備し，必要に応じて速やかに供給，使用できるかということを十分理解することは重要な点である．

1．術前輸血検査

輸血の可能性が考えられる症例では，種々の輸血検査が行われるがその意義，意味については意外と理解されてないことが多く，結果的に迅速な輸血がなされないことがあるので，輸血検査の意味について基本的な点を述べることとする．

血液は生きた臓器であり，他人の血液を投与する同種血輸血は一種の臓器移植である．臓器移植にとっては組織適合性(検査)が不可欠であるが，輸血では特殊な場合を除いて組織適合性が問題にはされず，むしろ血液の(正しくは赤血球)の適合性が問題となる．赤血球表面には300～500種類の抗原(血液型と考えてよい)が存在しているが，輸血にとって必要な血液型はABO血液型，Rh血液型など約20種類にすぎない．とはいうものの，すべての血液型を知る必要はない．表1には基本的な輸血検査を示す．

すべての検査はかならず，異なる複数の検体を

表 1　基本的な輸血検査*

1．ABO 血液型
2．Rh(D)血液型
3．不規則抗体スクリーニング
4．輸血する血液の血液型(オモテ試験のみ)

*血液型の検査は同一患者の二重チェック(同一患者からの異なる時点での 2 検体で検査をする)，同一検体の二重チェック(同一検体について異なる 2 人の検者がそれぞれ独立して検査をする)を必ず行うこと．

用いて行うことが必要である．また，同一検体を用いて複数の検査者が検査を行う必要もある．

ABO 血液型はもっとも基本となるものであり，赤血球表面の抗原を検出するオモテ試験，血液中の抗体を検出するウラ試験からなり，ごく一部の例外を除いてオモテ試験とウラ試験は一致する．たとえば，A 型では赤血球表面には A 抗原を，血中には抗 B 抗体を有する．これをランドスタイナーの法則という．

サイドメモ

通常の輸血と緊急輸血，そして異型輸血と不適合輸血

造血障害のような内科的患者への輸血は通常の輸血であり，ABO 型，Rh 型，不規則抗体スクリーニングそして狭義のクロスマッチを行ってなされるが，救命を目的とした緊急輸血では適合性を最優先することはあっても血液型はかならずしも同一である必要はない．そもそも異型輸血と不適合輸血は同意義ではない．異型輸血とは文字とおり異なる型の輸血をいい，通常は ABO 血液型の場合を指し，不適合輸血とは患者のもつ抗体と輸血される血液，とくに赤血球との間の抗原抗体反応の結果，溶血反応が生じ死亡に至る場合を含む副作用を生じる輸血をいい，すべて異型輸血である．しかし，異型輸血がすべて不適合輸血とは限らず，たとえば O 型赤血球を A 型に，あるいは A 型赤血球を AB 型に輸血する場合などは異型輸血ではあるが，抗原抗体反応は起こらず不適合輸血ではない．緊急輸血では救命第一で，同型であることに固執して過少輸血になりその結果患者の死を招くことは絶対行ってはいけない．異型ではあっても適合する赤血球製剤を確保して救命をはかるべきであり，もちろん同型の赤血球が入手すればその時点で切り変える．すなわち，緊急輸血時には異型輸血であっても不適合輸血にはならない赤血球輸血を行い，患者の救命を第一とすべきである．

Rh 型検査は赤血球表面抗原の検出を行うもので，通常は Rh(D)抗原の有無を調べるが，日本人では約 99.7%で Rh(D)抗原は陽性である．

不規則抗体とは ABO 血液型以外の輸血にとって意味のある(溶血反応を起こす)抗体で，約 20 種類存在する．上述した Rh(D)血液型に対する抗体も不規則抗体であるが，Rh 血液型を独立して検査をするのは，不規則抗体のなかでももっとも頻度が高く，また副作用も強いからである．

輸血される血液の血液型の検査を行う理由については項を改めて述べるが，通常は ABO 型で十分である．

2. 赤血球輸血ができること：適合性とは

(「サイドメモ」参照)

以上輸血のためにいくつかの検査を行ってきたが，ではそれらは適合性という観点からはいかなる意味を有するかを検証する．

輸血ができるために必要十分な条件は，患者(受血者)のもつ抗体と反応しない抗原の血液を選択し，確認することである．つまり重要なことは患者がいかなる抗体を有し，輸血される血液がいかなる抗原を有し，この 2 者間で抗原・抗体反応が起こらないことである．では患者はいかなる抗体を有するかといえば，まず，ABO 血液型の抗体(自然抗体，規則抗体という；もちろん AB 型患者は抗体を有しない)と不規則抗体である．ABO 血液型の抗体は先天的に有しており，血液型違いの造血幹細胞移植を受けた患者以外，変化することはない．不規則抗体は前述したように，Rh 型を含む約 20 種類の抗体で，先天的ではなく，輸血，妊娠など後天的に産生される．

3. ABO血液型抗体と不規則抗体の意義の差

(表 2)

ここできわめて重要なことは，血液型の抗体といっても，ABO 血液型抗体と不規則抗体のもつ臨床的意義はまったく違うことである．

ABO 血液型抗体と反応する抗原が輸血された ABO 型不適合輸血では，抗原抗体反応の結果，輸血された赤血球は補体により破壊され(血管内溶血反応)，ヘモグロビンが血中に放出される．大量の遊離ヘモグロビンは腎尿細管に沈着して腎障害，腎機能不全を，また大量に放出された K^+ イ