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## Long Lasting IgG Subclass and Antibacterial Polysaccharide Antibody Deficiency After Allogeneic Bone Marrow Transplantation

By Pierre Aucouturier, Anne Barra, Liliane Intrator, Catherine Cordonnier, Dominique Schulz, Françoise Duarte, Jean-Paul Vernant, and Jean-Louis Preud'homme

Serum IgG subclasses were measured by a competitive indirect immunoassay with monoclonal antibodies in 31 leukemic patients before and after bone marrow transplantation. Antibodies to *Hemophilus influenzae* type b (Hib) capsular polysaccharide were determined in 28 cases. Abnormally low or borderline subclass (mostly IgG2 and IgG4) levels were found late after transplant in 23 infected and noninfected patients. These levels persisted for as long as 25 months, in association with low or borderline IgA levels in 78% of the cases. IgG2, IgG4, and IgA often showed a parallel evolution, whereas IgG1, IgG3, and IgM often varied together in the opposite way. Class but not subclass deficiencies were more frequent in patients with

graft-v-host disease (GVHD). Subclass abnormalities predominated in infected patients, with mean levels correlating with the severity of infections; however, the abnormalities are not clearly predictive of infections in individual cases. Most patients with Hib pneumonia showed virtually no IgG antibody response to Hib, and one-half of the patients had a moderate IgM and IgA response. In the whole series, many sera collected >1 year after graft contained very low or undetectable antibodies. Correlation between anti-Hib antibody and IgG2 levels was significant but weak because of discrepancies that were only partially explained by the subclass distribution of the antibodies.

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**A** COMBINED cellular and humoral immunodeficiency affects patients after allogeneic bone marrow transplantation (BMT). Reconstitution is slow, and certain long-term survivors suffer severe and/or recurrent infections. Serum immunoglobulin (Ig) classes may be depressed for ~1 year for IgG and IgM and even longer for IgA, with a correlation between infections, Ig class deficiency, and chronic graft-v-host disease (GVHD).<sup>1-10</sup> IgG subclass deficiency is a common feature of primary immunodeficiency states. It predominantly affects IgG2 and IgG4 and may be observed as a "selective" deficiency or in various immunodeficiency syndromes,<sup>11</sup> especially IgA deficiency occurring as an apparently isolated defect<sup>12-17</sup> or in ataxia telangiectasia.<sup>18-21</sup> A frequent pathogen in such patients is *Hemophilus influenzae* type b (Hib),<sup>11,22,23</sup> whose major antigen is the capsular polysaccharide polyribosylribitolphosphate (PRP).<sup>24</sup> This is not surprising, since IgG2 appears to be the predominant subclass of antibacterial carbohydrate antibodies (Ab).<sup>25-27</sup> The observation of a relatively high incidence of Hib pneumonia in our transplanted patients<sup>28</sup> led us to study serum IgG subclass and anti-PRP Ab levels in transplanted patients affected with Hib pneumonia. Sera from patients with other infections or without infections were studied as controls.

### PATIENTS AND METHODS

**Patients.** Nine patients who received allogeneic BMT and experienced Hib pneumonia were retrospectively selected for the study. In view of the results, 22 other transplanted patients who survived >90 days and in whom serial posttransplant sera were available also were chosen as control cases. None of the patients received any IgG therapy during the study. None of the control patients had experienced Hib pneumonia, and we purposely selected patients with or without GVHD, viral, or other bacterial infections. Consequently, patients were listed according to the nature of their infections (Table 1): patients infected with extracellular bacteria, mostly Hib (compatible with impaired humoral immunity) (7 cases); patients with viral and/or intracellular bacterial infections (suggestive of cellular immune defect) (10 cases; two further patients suffered pneumonia of unknown origin); patients with both types of infections (5 cases), including Hib pneumonia in 2 cases; and patients free of infections (7 cases). Chemotherapy regimens preceding the graft varied according to the type and staging of the leukemias and to the number

of relapses. The conditioning regimen uniformly consisted of cyclophosphamide (60 mg/kg on days -5 and -4) and total body irradiation (10 gray, with lung shielding above 8 gray). To prevent GVHD, methotrexate was given until day 102 to all patients receiving allogeneic BMT according to the Seattle regimen.<sup>1</sup> Furthermore, patient 16 received T-depleted bone marrow. Patient 29, the only patient who had received a syngeneic transplant, was not submitted to GVHD prophylaxis. GVHD was diagnosed and graded according to usual criteria.<sup>29,30</sup> No noninfected patient suffered GVHD. In contrast, most patients with repeated infections were affected with severe chronic GVHD.

**Measurement of immunoglobulin class and subclass levels.** Ninety-six sera were collected before transplant and after BMT (follow-up 4 to 25 months, mean 13.2 months). Ig class levels were measured by laser nephelometry. IgG subclass levels were determined in coded samples by a competitive indirect immunoassay (ELISA) with monoclonal Ab, as previously described.<sup>31,32</sup> Normal values<sup>15,31,32</sup> were established in a study of 129 to 186 sera from normal blood donors aged 20 to 50 years. Serum of the donors of bone marrow grafts was not examined. Values below or at the lower limit of the 95% percentile range of normal sera (ie, 4.0 mg/mL, 0.6 mg/mL, and 0.18 mg/mL for IgG1, IgG2, and IgG3; 6.1, 0.8, and 0.5 mg/mL for IgG, IgA, and IgM, respectively) are described below as subclass or class deficiencies. For IgG4, whose level differs according to sex,<sup>31</sup> a 95% percentile range limit can be defined in men only (0.03 mg/mL). IgG2 and IgG4 display very heterogeneous distributions in healthy subjects, and low normal values are likely to

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include deficiencies.<sup>32</sup> Borderline levels ( $\leq 0.95$  mg/mL for IgG2 and  $< 0.1$  mg/mL in both sexes for IgG4) are therefore considered in the analysis.

**Determination of anti-PRP antibody levels.** Anti-PRP Ab were measured in 79 sera from 28 patients (mean time between BMT and collection of the last serum studied was 14.3 months). PRP was prepared from culture supernatants by precipitation with a cationic detergent and further purification by saline and phenol extractions<sup>33</sup> and was coupled to tyramine according to the method of Anthony et al.<sup>34</sup> Microtitration plates were coated with PRP-tyramine (5  $\mu$ g/mL PRP in phosphate-buffered saline [PBS]) and saturated with 1% bovine serum albumin (BSA) in PBS containing 0.05% Tween-20. One-half of every plate was treated identically except that PRP was replaced by PBS (blanks). Sera diluted  $1/20$  in 0.5% BSA containing PBS-Tween were incubated for 90 minutes at 37°C in triplicates in the PRP-coated and control wells. The plates were washed six times in PBS-Tween and incubated with peroxidase-tagged goat antisera specific for human  $\gamma$ ,  $\alpha$ , and  $\mu$  Ig chains (Institut Pasteur Production, Paris). After washings, bound conjugate was revealed with *o*-phenylenediamine and H<sub>2</sub>O<sub>2</sub>, and optical densities (OD) were recorded on a microplate reader.<sup>31</sup> Each ELISA plate contained standard positive and negative sera, and, as a reproducibility test, three further known positive sera (interassay coefficients of variation were 9.8% for IgG Ab, 7.8% for IgA Ab, and 11.3% for IgM Ab). For every sample, the experiment was repeated on the same plate with serum previously incubated for 45 minutes with high-concentration (500  $\mu$ g/mL) PRP. Only specific OD (inhibited by PRP) were taken into account. Results were expressed in arbitrary units calculated from specific OD in PRP-coated wells after results on uncoated wells were deducted by comparing the same data with the positive and negative standard sera.

Due to lack of material, the subclass distribution of IgG anti-PRP Ab could be studied in four patients only. These experiments were performed by a procedure similar to that previously described except that bound anti-PRP Ab were revealed by subclass-specific mono-

clonal Ab followed by peroxidase-coupled rabbit IgG anti-mouse IgG extensively absorbed with human IgG, as described in detail previously.<sup>35</sup>

**Statistical analysis.** Ig and anti-PRP Ab levels in patients and controls were compared by the Student's *t* test when possible, or by the Mann and Whitney's test when the number of subjects was too small. Percentages were compared using the Chi-square test.

## RESULTS

Detailed results of measurement of Ig class and subclass and anti-PRP antibody levels are shown in Table 1. Before transplant, several patients had low (patients 4, 7, 8, and 26) or borderline (patients 18 and 19) IgG2 and/or IgG4 (patients 1, 2, 3, 6, 24, 28, and 31) levels. IgA and IgG3 were rarely depressed (patients 1, 5, and 28, respectively), whereas abnormally low IgM levels were noticed in patients 1, 4, 8, 12, and 18. None of these patients had any past history of abnormal infections. The evolution of the levels of the various Ig isotypes after BMT varied greatly from patient to patient. However, comparison of the curves drawn for each patient (not shown), revealed a strong tendency for certain isotypes to vary together: IgG1 and IgG3 showed a roughly parallel evolution in 68% of cases, IgG1 and IgM in 48% of cases, and IgG3 and IgM in 45% of cases. On the other hand, roughly parallel curves were observed for IgG2 and IgG4 (61% of cases), IgG2 and IgA (52% of cases), and IgG4 and IgA (48% of cases). Any other association between Ig isotypes was noted in  $< 19\%$  of cases. In contrast, IgG1 and IgG2 varied in the opposite way in 61% of cases. Consequently, IgG2 levels were lower in late ( $> 350$  days after transplant) than in early samples in 11 cases. Subclass deficiencies or borderline levels at the end of follow-up

**Table 1. Diagnosis, Infection Patterns, Serum Ig, and Anti-PRP Ab Levels**

Patient No.	Age/Sex (yr)	Donor (Age/Sex)	Diagnosis	GVH		Infections	Date	Serum Ig (mg/mL)								Anti-PRP Ab (U)		
				Acute	Chronic			IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4	IgG	IgA	IgM	
1	28/M	25/M	AML, 1st CR	0	0	<i>H influ</i> (pneumonia) (d 120)	d -7	7.3	0.15	0.24	7.1	1.25	0.28	0.045	33	5	3	
							d 169	15.8	0.85	0.88	13.3	0.75	0.37	0.01	—	—	—	
							d 401	21.6	0.84	2.78	20.2	0.06	0.34	0.09	14	4	14	
2	20/F	24/M	AML, 1st CR	Grade II	+	<i>H influ</i> (pneumonia) (d 352) <i>Ui</i> (pneumonia) (d 450)	d -8	11.4	0.95	0.86	11.5	2.3	0.7	0.06	37	18	22	
							d 7	10.9	1.24	0.91	7.9	1.6	0.56	0.07	—	—	—	
							d 504	11.6	0.83	1.24	9.1	1.4	0.8	0.03	14	6	9	
3	33/F	39/M	CML, chronic phase	0	++	<i>H influ</i> (pneumonia) (d 248)	d -3	10.6	2.74	1.83	6.6	3.1	0.41	0.002	70	63	32	
							d 253	M	0.7	4.15	42.5	1.55	1.05	0.08	8	5	12	
							d 392	M	0.9	2.11	31	1.6	0.25	0.039	2	18	1	
4	4/M	6/M	AML, 2nd CR	0	0	<i>H influ</i> (pneumonia) (d 240)	d -9	6.5	1.01	0.3	5.8	0.2	0.32	0.22	4	—	—	
							d 267	6.4	0.65	0.41	8.5	1.15	0.49	0.124	17	26	22	
							d 518	5.3	0.49	0.81	7.5	0.65	0.21	0.108	33	20	30	
5	31/F	34/M	AML, 2nd CR	Grade II	0	<i>H influ</i> (pneumonia) (d 380) <i>Ui</i> (pneumonia) (d 580)	d -6	11.3	2.0	1.08	9.0	1.4	0.04	0.21	23	44	11	
							d 750	29.0	1.29	2.28	34.0	1.8	0.45	0.20	—	—	—	
							d -8	8.0	1.83	0.47	8.2	2.7	0.54	0.09	47	3	8	
6	16/M	14/F	AML, 1st CR	Grade I	+	<i>K pn</i> (pneumonia) (d 167)	d 68	3.8	0.2	0.29	3.6	0.9	0.33	0.03	19	2	2	
							d 166	4.3	0.2	M	5.4	0.65	0.15	0.06	0	3	4	
							d -8	11.5	1.82	1.1	—	—	—	—	—	—	—	
7	25/M	32/F	AML, 1st RC	Grade III	+	<i>H influ</i> + <i>K pn</i> (pneumonia) (d 77) <i>H influ</i> + <i>Asp</i> + <i>S aureus</i> (pneumonia) (d 180)	d 0	—	—	—	4.3	0.3	0.31	0.11	1	5	14	
							d 140	M	0.27	0.37	6.0	0.75	0.37	0.07	10	0	2	
							d 176	M	0.19	0.28	2.9	0.75	0.3	0.06	10	0	18	
8	9/M	5/M	ALL, 1st RC	0	0	CMV (pneumonia) (d 70) Herpes-zoster (d 330)	d 0	5.0	0.5	0.12	5.2	0.5	0.3	0.41	9	12	4	
							d 252	9.2	0.35	0.73	10.9	0.1	0.43	0.06	4	7	3	
							d 8	8.5	1.5	0.55	7.3	2.0	0.22	0.03	11	11	4	
9	10/M	12/F	ALL, 2nd CR	0	0	CMV (pneumonia) (d 107)	d 169	7.7	0.7	0.46	8.6	0.8	0.26	0.08	10	5	2	
							d 363	9.6	0.93	0.93	8.75	1.4	0.4	0.59	3	7	5	
							d -7	12.8	3.72	0.77	9.75	4.3	0.69	1.8	19	—	—	
10	21/M	20/F	AML, 1st CR	0	++	<i>L. mo</i> (septicemia) (d 204) CMV (pneumonia) (d 410) <i>L. pn</i> (pneumonia) (d 690) PV (encephalitis) (d 755)	d 405	M	0.36	M	7.5	0.12	0.57	1.4	5	—	—	
							d 760	M	0.52	M	6.6	0.55	0.20	0.24	7	1	9	

Table 1. Diagnosis, Infection Patterns, Serum Ig, and Anti-PRP Ab Levels (Cont'd)

Patient No.	Age/Sex (yr)	Donor (Age/Sex)	Diagnosis	GVH		Infections	Date	Serum Ig (mg/mL)							Anti-PRP Ab (U)		
				Acute	Chronic			IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4	IgG	IgA	IgM
11	26/M	30/M	ALL, 1st CR	0	+	CMV (pneumonia) (d 90)	d -7	14.0	1.55	0.9	11.5	5.0	0.7	2.4	—	—	—
							d 12	11.0	1.61	1.1	7.6	4.25	0.38	1.53	26	7	16
							d 128	M	0.69	0.35	9.2	1.4	0.21	0.25	4	1	18
							d 273	M	0.68	1.07	9.1	2.4	0.50	0.33	6	1	10
12	22/M	27/M	AML, 1st CR	Grade I	+	Varicella (d 30) CMV (pneumonia) (d 131)	d -7	9.8	0.81	0.32	—	—	—	—	—	—	
							d 0	9.8	0.67	0.25	6.6	4.3	0.23	0.24	13	4	4
							d 112	8.5	0.3	1.4	5.7	2.2	0.43	0.06	16	8	10
							d 240	M	0.27	M	14.6	0.9	1.10	0.04	13	3	3
13	42/M	35/F	AML, 1st CR	Grade II	0	CMV (pneumonia) (d 120) Herpes-zoster (d 240)	d 7	9.0	1.24	0.87	6.4	2.2	0.25	0.18	35	10	9
							d 154	9.3	0.57	0.89	9.9	0.8	0.85	0.06	25	9	5
							d 700	9.2	0.68	0.69	8.25	0.9	0.57	0.34	23	4	9
							d -8	9.7	1.67	2.72	9.35	2.7	0.55	0.26	—	—	—
14	33/F	35/M	AML, 1st CR	0	0	CMV (pneumonia) (d 145)	d 153	10.7	1.17	1.42	17.5	1.55	0.61	0.13	—	—	—
							d 291	10.0	0.74	2.7	15.1	2.75	0.57	0.13	—	—	—
							d -9	11.6	0.88	1.04	10.7	3.15	0.84	0.43	101	26	34
							d 81	9.2	0.48	0.34	11.5	1.8	0.72	0.16	12	57	4
15	35/M	39/F	AML, 1st CR	0	0	Herpes-zoster (d 90)	d 216	11.7	0.6	1.6	13.4	0.3	—	0.014	6	9	6
							d 8	3.8	0.51	0.33	3.15	0.85	0.32	0.119	2	0	4
							d 68	8.3	0.64	0.23	6.75	1.45	0.43	0.215	7	0	4
							d 230	M	0.68	0.49	9.1	0.95	0.35	0.094	4	0	3
17	15/M	12/M	ALL, 1st CR	0	0	Herpes-zoster (d 185) Ui (pneumonia) (d 355)	d 5	7.4	0.87	0.41	5.7	1.85	0.27	0.16	13	—	—
							d 377	10.5	0.68	1.13	11.1	1.0	0.76	0.23	4	11	11
							d 474	7.6	0.41	0.72	7.0	1.2	0.58	0.17	14	—	—
							d -8	8.2	0.7	0.2	7.3	0.75	0.33	0.33	—	—	—
18	34/M	28/F	ALL, 4th CR	Grade II	+	Ui (pneumonia) (d 39) Ui (pneumonia) (d 164)	d 82	4.9	0.25	0.29	3.5	0.6	0.24	0.15	—	—	—
							d 353	M	0.22	0.29	15.7	0.25	0.24	0.026	—	—	—
							d -5	17.9	1.14	1.58	15.7	0.92	1.37	0.39	131	64	32
							d 358	8.6	0.26	0.92	9.1	0.35	1.25	0.12	175	11	5
20	28/M	29/F	CML, chronic phase	0	++	Herpes-zoster (d 310) AV (pneumonia) (d 360) Str. pn (meningitis) (d 520) Herpes-zoster (d 790) E. coli (septicemia) (d 855) Mumps (orchitis) (d 920)	d 102	2.4	0.13	M	2.65	0.6	0.28	0.04	25	13	14
							d 385	2.9	0.3	0.27	2.65	0.35	0.34	0.05	—	—	0
							d 432	3.6	0.25	M	4.0	0.05	0.50	0.05	0	0	0
							d -8	15.6	0.8	1.3	15.8	4.1	0.43	0.40	—	—	—
21	27/F	24/F	AML, 1st CR	Grade IV	+	CMV + Str. pn (pneumonia) (d 133)	d 109	M	0.29	M	4.4	0.85	0.36	0.04	—	—	—
							d 119	—	—	—	5.25	0.60	0.25	0.03	—	—	—
							d -8	14.3	1.8	2.67	16.5	1.5	0.75	0.48	61	40	77
							d 81	4.1	0.19	0.2	3.6	0.75	0.21	0.18	14	0	17
22	35/M	32/M	AML, 1st CR	Grade II	+	Herpes-zoster (d 185) H. influ (pneumonia) (d 369)	d 384	11.2	0.45	1.86	12.0	0.01	0.58	0.01	5	4	11
							d 662	13.4	0.41	1.82	12.0	0.05	0.55	0.045	4	1	27
							d 74	—	—	—	6.5	1.0	0.3	0.28	—	—	—
							d 204	M	0.61	1.68	10.8	0.8	0.52	0.026	1	9	19
23	29/F	30/M	CML, chronic phase	0	0	Herpes-zoster (d 125) H. influ (pneumonia) (d 180) chronic sinusitis (d 195)	d 285	18.8	1.19	1.35	21.3	0.55	0.64	0.09	3	—	27
							d -7	9.9	1.61	1.53	8.5	1.45	2.7	0.016	15	—	6
							d 377	M	0.95	1.43	28.9	0.75	0.68	0.058	34	11	3
							d 770	12.5	1.28	1.0	19.4	0.4	0.9	0.085	34	114	1
24	20/F	20/M	AML, 1st CR	0	0	varicella (d 370) H. influ (pneumonia) (d 760)	d -8	8.9	1.63	0.47	8.0	2.5	0.84	0.20	32	37	11
							d 77	6.1	0.98	0.32	1.7	1.7	0.60	0.063	14	14	7
							d 372	9.3	0.98	1.56	4.4	1.46	1.35	0.09	5	4	8
							d -8	17.6	1.19	0.74	12.7	0.6	0.90	0.08	56	1	27
25	11/M	14/F	AML, 1st CR	0	0	—	d 61	7.8	0.39	0.51	9.4	2.3	0.01	0.19	42	—	—
							d 369	6.6	0.51	0.42	6.1	0.85	0.65	0.04	3	0	1
							d -7	8.3	1.14	1.03	6.4	2.0	0.47	0.17	35	19	15
							d 97	5.0	0.2	0.43	4.3	0.7	0.24	0.07	16	0	1
26	15/F	17/M	AML, 1st CR	0	0	—	d 363	M	0.30	0.71	12.4	0.95	0.33	0.009	0	0	2
							d -8	9.2	0.71	0.54	7.2	2.4	0.01	0.029	4	4	12
							d 222	12.8	1.35	7.9	11.1	0.4	0.9	0.032	0	4	11
							d 450	7.2	2.07	1.52	7.2	1.7	0.13	0.13	3	5	7
27	16/F	14/M	ALL, 1st CR	0	0	—	d -118	15.3	2.15	2.33	16.5	2.9	2.1	1.11	31	70	51
							d 134	13.8	1.3	1.61	10.1	3.1	1.35	0.27	69	61	8
							d 293	9.9	0.96	0.69	11.1	2.9	1.1	0.185	35	51	14
							d -8	7.0	1.51	0.96	6.2	1.1	0.39	0.11	56	47	23
28	30/F	14/M	AML, 1st CR	0	0	—	d 91	7.2	1.24	0.2	7.6	2.6	0.51	0.09	34	18	15
							d 217	8.0	1.37	1.2	8.7	2.2	0.49	0.048	46	21	18
							d -8	9.0	0.7	0.54	6.5	1.5	0.38	0.085	13	3	7
							d 8	7.8	0.92	0.53	5.0	1.75	0.35	0.08	—	—	—
29	25/M	Syngeneic graft	CML, acute phase	0	0	—	d 113	7.9	0.1	0.23	3.5	1.0	0.39	0.037	13	0	4
							d 275	8.1	0.37	0.65	8.1	0.9	0.65	0.077	5	0	0
							d 522	M	—	—	6.7	0.7	0.62	0.08	0	0	0
							d -8	9.0	0.7	0.54	6.5	1.5	0.38	0.085	13	3	7

Boldface numbers represent abnormally low levels.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; H. influenza, *Hemophilus influenzae*; K. pn, *Klebsiella pneumoniae*; Asp., *Aspergillus fumigatus*; S. aureus, *Staphylococcus aureus*; CMV, cytomegalovirus; L. mo, *Listeria monocytogen*

predominantly affected IgG2 (20 patients) and IgG4 (19 patients), together with low or borderline IgA levels in 78% of cases.

The analysis of subclass levels in the last studied samples showed that long-term subclass deficiencies were observed predominantly in infected patients (only one noninfected patient had IgG4 deficiency). Every patient with an infection pattern compatible with both cellular and humoral ID was subclass-deficient, with a maximum follow-up of 25 months. Borderline levels were observed in all patients' groups, including noninfected subjects, in whom the incidence of complete recovery was the highest. Differences according to the infection patterns are reflected in the mean IgG subclass values in the last studied samples (Table 2). On the whole, IgG1 and IgG3 were higher and IgG2 and IgG4 lower than in normal subjects (differences between patients and controls were significant except for IgG3 levels in infected patients); the lowest values for the two latter isotypes were in patients with infections of both types (mean 0.33 and 0.08 mg/mL, respectively) and the highest in noninfected patients. Because of the small size of the group of noninfected patients, differences between infected and noninfected patients were significant for IgG2 levels only ( $P < .05$ ). No significant correlation was observed between the ages of the donors and recipients of the graft and the incidence of subclass deficiency.

Serum collected at periods close to infectious episodes was available in certain patients only. Comparison with subclass levels in the sera from noninfected patients showed an incidence of subclass deficiency possibly higher in infected patients (the difference is not significant in such a small series). Indeed, for IgG2, low levels were observed during 8 of 21 infectious episodes (4 with extracellular bacteria and 4 with intracellular bacteria or viruses) and borderline levels during 6 other episodes, whereas of 14 samples collected from noninfected subjects at similar periods after graft, one contained low and 5 contained borderline IgG2 levels. Despite this, the finding of normal subclass levels during one-third of the infectious episodes and the rare but possible occurrence of low levels in noninfected patients make the finding of subclass deficiency suggestive but not predictive of occurrence of infection in individual cases.

Comparison of serum Ig levels in patients with and without GVHD clearly shows that class deficiencies occurring late after BMT were observed predominantly in chronic GVHD: Only patients with chronic GVHD had total IgG and IgM deficiencies, and IgA deficiency was more frequent

in GVHD (75% v 32% of cases,  $P < .02$ ). As for IgG subclasses, the incidence of deficiency did not differ according to the presence or absence of acute or chronic GVHD. However, the patient who received a syngeneic graft (patient 29) is one of the only two patients in whom every isotype was at normal or high levels throughout the study.

Six of nine patients affected with Hib pneumonia had abnormally low or borderline serum IgG2 levels, an incidence that is not different from that observed in patients in whom Hib pneumonia could not be demonstrated. This led us to determine serum levels of anti-PRP Ab. Before transplant, patients 4 and 7, who had low IgG2, also had low Ab levels (Table 1). Mean Ab levels before graft, calculated excluding patients with IgG2 deficiency, were similar in the different patient groups and comparable to those in normal adults. We had enough material to study anti-PRP Ab at the moment of Hib pneumonia in only two patients (patients 3 and 7); their levels were low although IgG2 was in the normal range in case 3. After Hib infection, IgG anti-PRP Ab remained low or continued to decrease except in patients 4 and 24, in whom they reached levels comparable to those in normal subjects without known Hib infection. Patient 7, who showed a poor response after Hib pneumonia, experienced a second bout of Hib infection 3 months later. Mean IgG anti-PRP Ab level was not higher in patients infected with Hib than in the other patients under study (Table 3). Patients 4 and 24 had low IgG2 levels. Due to lack of material, we could not study the subclass distribution of these IgG Ab. This experiment was performed in patient 1 at day 401; the patient's serum contained subthreshold levels of IgG2 and low but detectable IgG anti-PRP Ab. Two-thirds of these Ab belonged to the IgG1 subclass, and one-third belonged to IgG2.

A moderate increase in IgM and IgA Ab was observed just after the pneumonia in four and three cases, respectively. A strong IgA response was manifested by one case. Consequently, mean IgM and IgA Ab levels after Hib infection were similar to normal subject levels (Table 3).

Most patients without known Hib infection had low anti-PRP Ab of the three classes, the latest samples studied often showing the lowest values. A number of sera collected after 1 year contained no detectable Ab or levels similar to those in young children (Tables 1 and 3). However, there were exceptions, such as patients 19, 29, and 30. Patient 19 had high Ab levels before transplant and 1 year later, despite a very low IgG2 level. This striking contrast led us to study the subclass of the Ab in the sample collected at day 358. In fact, we found that anti-PRP Ab in this serum was restricted to

**Table 2. Serum IgG Subclass Levels in BMT Patients and Controls**

Subjects	n	IgG1	IgG2	IgG3	IgG4
<b>BMT</b>					
All patients					
Before graft	25	9.24 ± 3.63	2.12 ± 1.33	0.66 ± 0.59	0.39 ± 0.56
Last sample	31	11.49 ± 7.19	1.01 ± 0.77	0.58 ± 0.33	0.12 ± 0.12
Infected patients, last sample	24	12.49 ± 7.94	0.86 ± 0.73	0.50 ± 0.28	0.125 ± 0.135
Noninfected patients, last sample	7	8.09 ± 2.63	1.54 ± 0.74	0.83 ± 0.38	0.08 ± 0.06
Normal adults	129-186	6.43 ± 1.50	2.64 ± 1.36	0.42 ± 0.17	0.39 ± 0.38

Values are mean ± SD, mg/mL.



Table 3. Anti-PRP Ab Levels in the Last Studied Samples From BMT Patients and in Control Sera

Subject	IgG			IgA			IgM		
	n		Range	n		Range	n		Range
BMT									
All patients	27	17	(0-175)	25	12	(0-114)	25	9	(0-30)
<i>Hemophilus influenzae</i>	8	14	(2-34)	7	23	(0-114)	8	16	(1-30)
No <i>Hemophilus influenzae</i>	19	18	(0-175)	19	7	(0-51)	19	6	(0-18)
Normal children aged 12-25 mo	10	3	(0-10)	10	2	(0-12)	10	8	(2-15)
NHS pool*	1		60	1		21	1		21
Normal adults									
Before	5	32	(0-76)	5	33	(10-71)	3	33	(29-35)
3 weeks after vaccination†	5	113	(36-235)	5	169	(39-323)	5	73	(44-100)

Values are units, means, and ranges. Ab levels in patients were significantly lower than in normal (nonvaccinated) subjects. Due to the small size of the groups, differences between Hib-infected and non-Hib-infected patients are not significant.

\*Normal human sera from 60 adult blood donors.

†One injection of PRP (25 µg).

IgG2. Two other sera with fair Ab and low IgG2 levels were studied for subclass distribution (patient 20 at day 102 and patient 26 at day -8), and the Ab were equally distributed in the IgG1 and IgG2 isotypes. The correlation between IgG2 and anti-PRP Ab in the whole study, although significant ( $P < .05$ ), was weak ( $r = .23$ ).

#### DISCUSSION

The present study shows that IgG subclass deficiencies occur with a very high frequency in long-term survivors after BMT. They predominantly affect IgG2 and IgG4, as in a variety of primary and acquired immunodeficiency syndromes.<sup>12,15</sup> Similar findings were recently reported in abstract form.<sup>36</sup> A striking observation in our study is that IgG2-IgG4 deficiencies, often associated with low IgA levels, frequently developed late after transplant, whereas IgM, IgG1, and IgG3 and total IgG had reached normal or high levels. Indeed, IgG2, IgG4, and IgA often showed a parallel evolution, whereas IgG1, IgG3, and IgM tended to vary together in the opposite way. This is reminiscent of several observations: in childhood, the increase of serum IgG1 and IgG3 levels is rapid and follows total IgG, whereas IgG2 and IgG4 reach adult levels only around puberty (as IgA does)<sup>37-39</sup>; in common variable immunodeficiency subclass imbalance is very common, with predominant deficiencies of either IgG2 and IgG4 or IgG1 and IgG3<sup>15</sup>; patients with "selective" IgA deficiency often have IgG2-IgG4 deficiency, with frequent IgG1-IgG3 increase in infected patients.<sup>12-17</sup> These subclasses also differ with respect to Ab specificity, with an IgG1-IgG3 predominance of Ab to viral proteins<sup>40-43</sup> and an IgG2 predominance of antibacterial polysaccharide Ab.<sup>25-27</sup> Finally, studies of in vitro B cell maturation are compatible with different regulations of IgG2-IgG4 and IgG1-IgG3 expression.<sup>44-46</sup>

The asynchronous evolution of the subclasses and the well-known existence of profound T cell disturbances after BMT<sup>1-6,47-50</sup> suggest that subclass deficiency might result from an impaired T cell regulation rather than from an intrinsic B cell defect. Experimental work in the mouse<sup>51,52</sup> favors the hypothesis that the expression of the isotypes

whose genes are located downstream in the  $C_H$  locus (as IgG2 and IgG4 are in humans) requires more T cell help than does control of upstream isotypes. The finding of IgG2-IgG4 deficiency in human syndromes featuring impaired T-B cell cooperation, such as the Di George's syndrome, the severe combined immunodeficiency syndrome with abnormal expression of HLA class II antigens, ataxia telangiectasia, and AIDS<sup>15,19,21,53</sup> is in keeping with this hypothesis. Although bacterial polysaccharides are T-independent antigens, antipolysaccharide Ab production is highly dependent on T cell regulation.<sup>54</sup> Therefore, both subclass and anti-PRP Ab deficiencies may result from abnormal T cell function. Cells from five of the present patients were studied for in vitro suppressor activity.<sup>50</sup> There is no correlation between excessive suppressor activity and the present findings, suggesting that impaired helper function might play a major role.

Previous work<sup>1-10</sup> showed that GVHD is a significant factor in the occurrence of infections and of Ig class deficiency; this is confirmed in the present study. In contrast, we observed an incidence of subclass deficiency similar in patients with and without GVHD. However, the finding of fully normal Ig levels throughout the study was exceptional and concerned virtually only the patient who received a syngeneic transplant. Therefore, that clinically undetectable GVHD plays a role in the pathogenesis of subclass deficiencies is a possibility. Both the mean subclass levels and incidence of subclass deficiencies differed according to the infection patterns. Subclass deficiencies were observed in patients infected with extracellular bacteria as well as in patients with viral or intracellular bacterial infections in whom they are unlikely to play a direct role. They were constant in patients with both types of infections and may reflect the general level of immunodeficiency in these patients. The subclass deficiencies may contribute to the occurrence of extracellular bacterial infections, but certain patients free of infections had low or borderline subclass levels, whereas some infected patients had normal class and subclass levels at the period of infectious episodes. The explanation of the occurrence of infections is therefore more

complex than a mere subclass deficiency, even in patients with Hib pneumonia. Anti-PRP Ab defect might play some role, since we observed low levels just before pneumonia in a patient with normal IgG2 level and since there was a very poor IgG Ab response after pneumonia (protection against Hib is predominantly mediated by IgG Ab<sup>35</sup>). One patient with low IgG response experienced a second bout of Hib pneumonia 3 months later. Several patients who had no Hib pneumonia developed anti-PRP Ab (patients 19, 24, 29, and 30), but we do not know whether the other patients without pneumonia have been infected by Hib. Humoral immunodeficiency thus probably plays a role in the genesis of infections observed in BMT recipients. Thus, substitutive IgG therapy of infectious episodes may be indicated even in patients without class and/or subclass deficiency. Whether a prolonged systematic IgG treatment is indicated for prophylaxis of infections remains to be determined. On the other hand, the high incidence of Hib pneumonia in our series<sup>28</sup> and the defective anti-PRP Ab response raises the questions of the indication and timing of vaccination in transplanted patients. In such cases, a protein conjugate PRP vaccine should be used, since it is effective in IgG2-deficient patients who do not respond to PRP alone.<sup>36</sup>

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## **Long lasting IgG subclass and antibacterial polysaccharide antibody deficiency after allogeneic bone marrow transplantation**

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