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# Kinetics of Anti-*Campylobacter jejuni* Monomeric and Polymeric Immunoglobulin A1 and A2 Responses in Serum during Acute Enteritis

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**The intensity and kinetics of the serum polymeric and monomeric immunoglobulin A1 (IgA1) and IgA2 antibody responses to *Campylobacter jejuni* were analyzed. A rapid and marked serum IgA antibody response involving both the monomeric and polymeric components of IgA was observed after *C. jejuni* infections. IgA antibodies reached a peak of activity in serum during week 2 after the first symptoms of enteritis, about 10 days before the peak of IgG activity. Polymeric IgA accounted for most of the anti-*C. jejuni* activity at the peak of the IgA response (median, 90%; range, 44 to 98%) but rapidly disappeared from serum over a few weeks. In contrast, the serum monomeric IgA antibody response was low and was maintained over a prolonged period of time. Anti-*C. jejuni* IgA detected in the serum of healthy blood donors was mainly monomeric (median, 83%; range, 17 to 94%). In both the patients and the positive controls, IgA1 was the predominant (>85%) subclass involved, even when the IgA antibody response was mainly polymeric. Our results suggest that polymeric IgA antibody responses are linked to a strong or persisting antigenic stimulation or both. Polymeric IgA antibodies appear to be a potential marker of acute *C. jejuni* infections, and their determination could provide a useful tool for the serological diagnosis of recent *C. jejuni* infections.**

Despite a low concentration in serum of immunoglobulin A (IgA) as compared with IgG, IgA appears to be a major component of circulating immunoglobulins (19), since the absolute amounts of IgA and IgG delivered to plasma each day are relatively similar (12, 25). Human IgA is represented by two subclasses (IgA1 and IgA2) and two molecular forms (polymeric and monomeric). Serum IgA occurs predominantly in the monomeric form (90%) (12, 15) and has a relatively larger proportion of IgA1 molecules (85 to 90%) (9, 12) than do external secretions, which contain almost exclusively polymeric IgA (90%) (15, 24) and have a nearly equal distribution of IgA1 and IgA2 (40% IgA2) (11). Whereas there seems to be no clear-cut subclass restriction of IgA antibody responses to antigens (7), IgA antibodies appearing in serum during acute viral infections are predominantly polymeric (1, 6, 18, 21). The molecular size of serum IgA antibodies appearing during other antigenic stimulations has not been reported and could depend on the nature of the antigen and the route of immunization. In this study we analyzed the magnitude and kinetics of the serum monomeric and polymeric IgA1 and IgA2 antibody responses during *Campylobacter jejuni* enteritis, chosen as a model of infection of the mucosal surfaces by invasive bacteria. *C. jejuni* is the most common bacterial cause of acute diarrheal illness in developed countries (4), and enteritis results in the appearance in serum of IgG, IgM, and IgA antibodies (3).

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## MATERIALS AND METHODS

**Patients.** Two groups were investigated: one group included 111 patients with acute *C. jejuni* enteritis, proven by coproculture, and the other was a control group which included 327 blood donors. In all 111 patients with *C. jejuni* enteritis, blood samples were obtained between 5 and 14 days after clinical onset of the disease; second and third blood samples were obtained from 74 of 111 and 46 of 111 patients, respectively. These 111 patients were selected from (i) the pediatric clinic of the Saint-Pierre Hospital of Brussels ($n$ = 21; age, 0.2 to 6 years; mean age, 1 year), (ii) the Municipal Public Health Service of Rotterdam ($n$ = 69; age, 4 to 76 years; mean age, 32 years), and (iii) a group of young Dutch soldiers who simultaneously contracted their disease during a military survival exercise ($n$ = 21; age, 19 to 26 years; mean age, 21 years). The control group included 271 clinically healthy blood donors (age, 18 to 60 years; mean age, 39 years) and 56 children (age, 0.1 to 17 years; mean age, 8 years) who required blood analysis for medical reasons other than gastrointestinal infections or immunological disorders.

**Anti-*C. jejuni* radioimmunoassay. (i) Antigen.** *C. jejuni* antigen was kindly provided by the Institut Virion (Rüschlikon, Switzerland). It was derived from five *C. jejuni* strains (LAU7, LAU25, LAU51, PEN15, and PEN17) and was prepared by means of extraction at high pH as previously described (20). Briefly, cultured cells were extensively washed in phosphate-buffered saline (PBS), and the cell sediment was suspended at 2% (vol/vol) in 0.1 M glycine buffer (pH 9.8). After brief sonification, antigen extraction was performed by incubation of this suspension for 12 h at 4°C under gentle agitation. Finally, 2% bovine serum albu-

min (wt/vol) was added before lyophilization for stabilization of the antigen.

This antigen has already been extensively used for *C. jejuni* serology in a complement fixation test that proved its specificity (20, 22). Its suitability as a "common *C. jejuni* antigen" has been shown by demonstration of its reactivity with 33 rabbit antisera raised against 33 different *C. jejuni* serotypes (S. Lauwers, Ph.D. thesis, Free University of Brussels, Brussels, Belgium, 1985). Finally, its antigenic components have been analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis by H. Goossens (personal communication), revealing the presence of approximately 30 different polypeptide bands, the major ones being at 45,000 and 60,000 daltons, as previously reported by Logan and Trust (17).

**(ii) Radioimmunoassay.** Antibody titers were measured by a solid-phase radioimmunoassay. *C. jejuni* antigen (500 μg/ml) diluted in PBS (pH 7.2) was actively absorbed for 16 h at 20°C to polystyrene cups coated with rabbit anti-*C. jejuni* IgG (25 μg/ml in PBS). After being washed, the cups were incubated for 2 h with PBS supplemented with 5% (vol/vol) horse serum and then for 16 h at room temperature with serum samples diluted in PBS supplemented with 5% (vol/vol) horse serum and 0.05% Tween 20. The serum dilutions were 1/50 for IgA and 1/100 for IgG. After being washed again, the cups were filled with $^{125}$I-labeled mouse monoclonal IgG1 anti-human alpha-chain antibodies or $^{125}$I labeled affinity-purified goat anti-human gamma-chain antibodies. The goat antiserum was passed through a column of Sepharose-bound whole rabbit serum to avoid cross-reactions with rabbit IgG. After incubation for 16 h at 20°C and a final washing, the radioactivity bound to the solid phase was counted. Results were expressed in arbitrary units (AU) by reference to standard curves established by serial dilutions of positive reference sera. To avoid nonspecific binding caused by the presence of IgA rheumatoid factor or IgA anti-bovine serum albumin antibodies (which might be detected by the bovine serum albumin present in the *C. jejuni* antigen), we tested all samples in parallel on (i) cups coated with anti-*C. jejuni* rabbit IgG only or (ii) anti-*C. jejuni* rabbit IgG–2% bovine serum albumin. Six individuals, five children and one adult (five controls, one with enteritis), were excluded from the study because more than 15% of their anti-*C. jejuni* IgA activity was caused by these nonrelevant bindings.

**Specificity and sensitivity.** The specificity was assessed by absorptions of eight positive sera from patients with acute *C. jejuni* enteritis and eight positive sera from healthy controls. Anti-*C. jejuni* IgA was measured in parallel before and after three successive incubations with each of the following pools of freshly cultured bacteria: *C. jejuni*, *Campylobacter fetus* subsp. *fetus*, *Salmonella* sp., or *Escherichia coli*. The four pools of bacterial strains were adjusted to $23 \times 10^8$ CFU/ml. After each incubation with the bacteria (8 h, 4°C), sera were centrifuged at 12,000 × *g* for 15 min. After the absorptions, the supernatants were adjusted to a final 1:50 dilution in PBS supplemented with 5% horse serum and 0.05% Tween 20 and were tested for anti-*C. jejuni* IgA. The 16 sera were tested before and after absorption in five different experiments. For both the patients and the controls, the antibody titers dropped significantly only after absorption with *C. jejuni* strains (Fig. 1). In addition, to exclude the possibility of cross-reactions with only some strains within each bacterial species, we carried out more absorptions with the eight positive healthy control sera using 3 different *Proteus* strains, 2 *Yersinia* strains, 4 *Shigella* strains, 4 *Salmonella* strains, and 10 different enteropathogenic *E. coli* strains. Except for the partial absorption of one serum sample after incubation with two different *Proteus* strains, no significant reduction of the anti-*C. jejuni* titer was observed in the presence of each of these bacteria.

The positivity limits of the assays were defined by the mean plus three standard deviations of the results obtained for 16 positive sera after specific absorptions.

**Monomeric and polymeric IgA antibodies.** The molecular size distribution of the specific serum IgA antibodies was analyzed by ultracentrifugation as previously described (12). Only sera containing more than 40 AU of anti-*C. jejuni* IgA antibodies could be accurately analyzed by this technique. Sera from 25 patients with acute *C. jejuni* enteritis (4 children and 21 adults), from 1 patient with acute *C. jejuni* septicemia, and from 9 healthy controls with positive IgA anti-*C. jejuni* antibodies were ultracentrifuged. Serum samples (60 μl) diluted 1:5 in PBS were applied on top of isokinetic 5 to 21% (wt/wt) sucrose gradients (12-ml tubes) and centrifuged for 16 h at 38,000 rpm in an SW-40 Ti swinging bucket rotor in a Beckman Spinco L2-65B ultracentrifuge. Sucrose gradients were done either in PBS or in 0.1 M glycine hydrochloride-buffered saline (pH 3.0). After centrifugation, 30 fractions of 0.4 ml were collected by downward elution of the gradients and were then immediately diluted 1:5 in PBS containing 5% horse serum and 0.05% Tween 20. Anti-*C. jejuni* IgA was measured in each fraction by using the assay described above. Total IgA concentrations were determined in the fractions by using the immunoradiometric assay for IgA described previously (10). Proportions of polymeric IgA and monomeric IgA were measured by planimetry. In a few cases, the binding of antibodies to the antigen-coated cups was measured in all gradient fractions with $^{125}$I labeled polyclonal anti-secretory component antibodies (13).

**IgA1 and IgA2 antibodies.** The IgA1 and IgA2 fractions of serum IgA antibodies were measured by the same assay as used to measure total anti-*C. jejuni* IgA, except that $^{125}$I-labeled mouse monoclonal anti-IgA1 (DLDB4) and anti-IgA2 (DLDD2) antibodies were used instead of $^{125}$I-labeled anti-alpha-chain antibodies. The characterization of these monoclonal antibodies has been previously reported (14). Data were expressed in AU of anti-*C. jejuni* IgA1 or IgA2 based

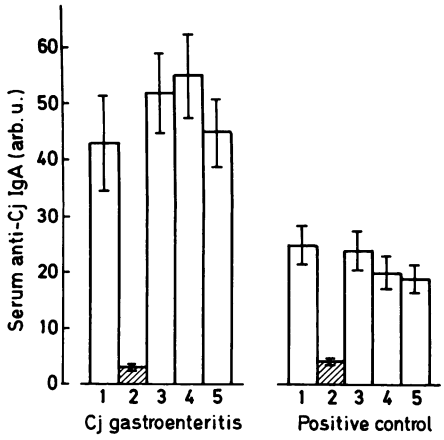


FIG. 1. Serum anti-*C. jejuni* (Cj) IgA antibody titer before (1) and after absorption with pools of *C. jejuni* (2), *C. fetus* subsp. *fetus* (3), *Salmonella* sp. (4), and *E. coli* (5). Columns indicate the mean ± standard deviation of five independent absorptions of the same serum. arb. u. = AU.

on standard curves obtained by incubating the same amount of $^{125}$I-labeled monoclonal antibodies in plastic cups coated with increasing and equivalent (as demonstrated with $^{125}$I-labeled anti-alpha-chain antibodies) amounts of IgA1 or IgA2 myeloma proteins. Because it is recognized that monoclonal antibodies directed against the same antigen may have different association constants and fine specificities, the results obtained with the DLDB4 and DLDD2 antibodies were compared with those obtained with three other sets of monoclonal anti-IgA subclass antibodies, 1-155-1 and 14-3-26 (9), DLDA7 and DLDB7 (14), and 69.114 and 16.512 (14).

**Statistical analysis.** Analysis of anti-*C. jejuni* IgA and IgG antibody titers in serial blood samples (mean ± standard error of the mean) was performed after log transformation of the data. Correlations between antibody titer and age of individuals were assessed by the Spearman rank test. Results of size and subclass distributions of specific IgA were expressed by medians, and comparisons between different groups were performed by the Mann-Whitney U test or the Wilcoxon test for paired values (23).

## RESULTS

**Kinetics of the serum IgA antibody response to *C. jejuni*.** The kinetics of serum IgA responses to *C. jejuni* were analyzed from data obtained from 65 patients with anti-*C. jejuni* IgA and from whom two or three serial blood samples were collected over the first 3 months after the clinical onset of enteritis (Fig. 2). Specific IgA was detected in serum as soon as 5 days after the first symptoms. The highest titers were recorded during week 2, and then antibody titers rapidly fell. On day 25, 38% of the patients no longer had specific serum IgA, and only low IgA titers were detected in positive sera (mean, 11 AU; range, 9 to 14 AU). The IgA antibody response differed from the IgG antibody response in two respects: it appeared more quickly and was shorter-lived (Fig. 2).

**Serum anti-*C. jejuni* IgA in patients with acute *C. jejuni* enteritis as compared with controls.** The incidence of anti-*C. jejuni* IgA in the serum of 111 patients with acute *C. jejuni* enteritis (blood samples taken between 5 and 14 days after the onset of diarrhea) as compared with control individuals (random serum) is shown in Fig. 3. Anti-*C. jejuni* IgA was detected in an average of 88% of patients with acute

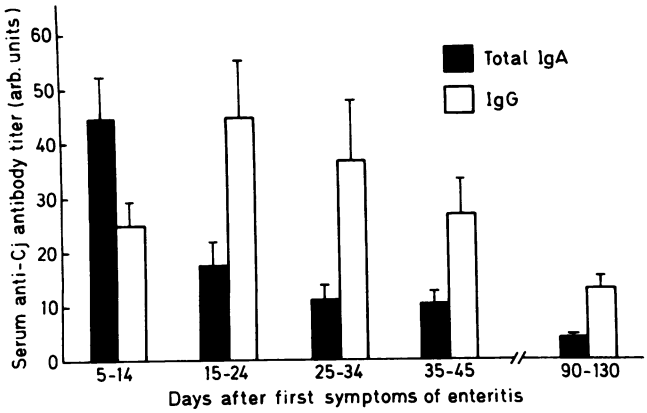


FIG. 2. Kinetics of the serum anti-*C. jejuni* (Cj) IgA and IgG antibody responses in 65 patients with anti-*C. jejuni* IgA and from whom two or three serial blood samples were collected over the first 3 months after the clinical onset of enteritis. Columns indicate the geometric mean ± standard error of the mean. arb. units = AU.

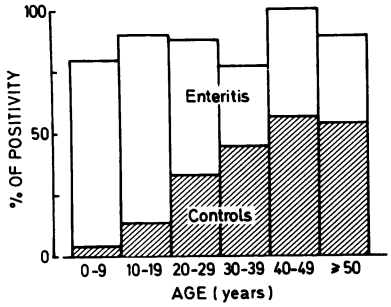


FIG. 3. Incidence of anti-*C. jejuni* IgA antibody seropositivity in patients with acute enteritis (open columns) and controls (hatched columns) in relation to age.

enteritis, whatever their distribution into six classes of age. In controls, however, the frequency of detection of anti-*C. jejuni* IgA increased with age, from 4% before 10 years to 54% after 50 years; however, anti-*C. jejuni* IgA titers did not correlate with age. Although median IgA titers were higher in patients with acute enteritis than in positive controls (34 versus 18 AU), large overlaps were seen between the ranges of both groups (7 to 400 AU versus 7 to 84 AU, respectively).

**Size distribution of serum anti-*C. jejuni* IgA antibodies in patients with acute *C. jejuni* infections as compared with controls.** The respective contributions of monomeric IgA and polymeric IgA to anti-*C. jejuni* IgA in patients with acute *C. jejuni* infections versus positive controls are shown in Fig. 4. At the peak of the IgA response following acute enteritis, polymeric IgA accounted for most of the IgA activity (median, 90%; range, 44 to 98%), whereas total serum IgA was mainly monomeric (median, 84%; range, 74 to 98%). Even during acute *C. jejuni* septicemia, 96% of anti-*C. jejuni* IgA was polymeric (Fig. 5, case 1). In positive controls, however, polymeric IgA constituted only 17% (6 to 83%) of serum anti-*C. jejuni* IgA, with most of the IgA activity being found in the 7S monomeric IgA fraction. The kinetics of the serum monomeric and polymeric IgA responses could be analyzed separately in three cases of enteritis (Fig. 5, cases 2 through 4) and in the *C. jejuni* septicemia case (Fig. 5, case 1) by analyzing the sizes of anti-*C. jejuni* IgA in samples taken both during week 2 and at 1 month after onset of the disease. In these four individuals, the small peak of anti-*C. jejuni* monomeric IgA detected at 5 to 14 days was maintained 2 to 3 weeks later, whereas most of the circulating polymeric IgA antibodies had disappeared. As shown by the sedimentation profiles, serum polymeric IgA antibodies in both patients with acute enteritis and positive controls were made up mainly of 10.2S dimeric IgA. These dimeric IgA antibodies were not complexed with secretory component, as demonstrated by the absence of a reaction when labeled anti-secretory component antibody was used in the anti-*C. jejuni* assay. The sedimentation profile of serum anti-*C. jejuni* IgA was not significantly modified when samples were centrifuged at an acid pH, indicating that these 10.2S anti-*C. jejuni* IgA antibodies were not IgA immune complexes.

**Anti-*C. jejuni* IgA1 and IgA2 antibodies.** The respective contributions of IgA1 and IgA2 to anti-*C. jejuni* IgA were assessed in 11 patients with enteritis and in 9 controls whose serum had been analyzed by ultracentrifugation. Irrespective of the molecular size distribution, serum anti-*C. jejuni* IgA was made up mostly of IgA1 in both enteritis patients (median, 82%; range, 64 to 96%) and controls (median, 85%; range, 79 to 90%) when anti-IgA1 DLDB4 and anti-IgA2 DLD2 were used. The results obtained with the three other

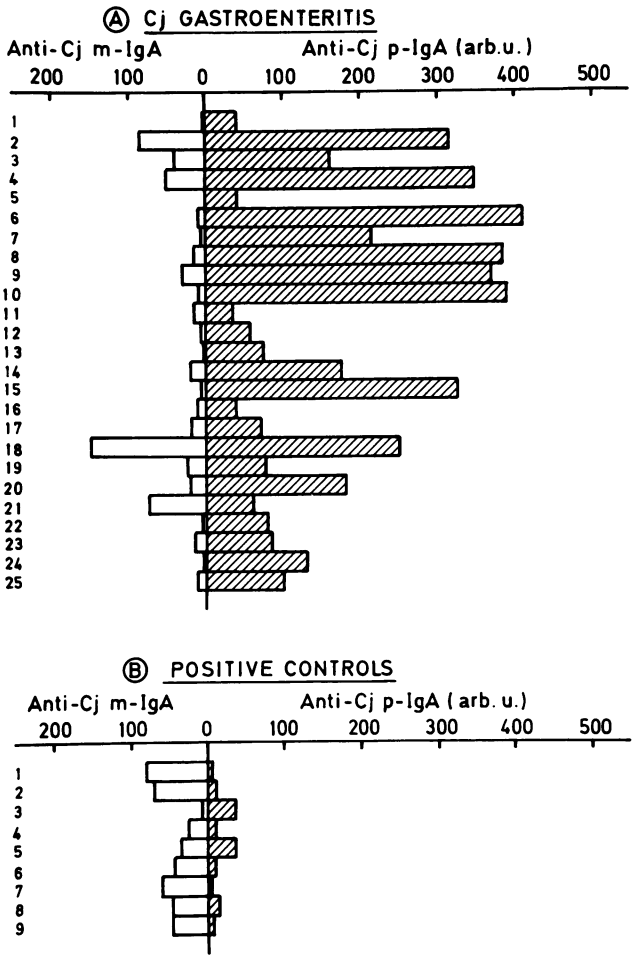


FIG. 4. Individual anti-*C. jejuni* (Cj) monomeric IgA (m-IgA) and polymeric IgA (p-IgA) antibody titers in 25 patients with acute enteritis (A) (patients 1 to 4, children; patients 5 to 25, adults) as compared with 9 positive healthy controls (B). arb. u. = AU.

sets of monoclonal antibodies varied by means of 6.4% (1-155-1 and 14-3-26), 6.5% (DLDA7 and DLDB7), and 9.7% (69.114 and 16.512). To further demonstrate the independence between the molecular size distribution and the subclass distribution of specific IgA, we measured in all gradient fractions from two patients the binding of antibodies to antigen-coated cups with $^{125}$I-labeled monoclonal anti-IgA1 antibody DLDB4. As with total IgA, anti-*C. jejuni* IgA1 was mainly associated with polymeric IgA.

## DISCUSSION

The polymeric form of IgA antibodies in serum has been previously reported during rubella, measles, varicella, herpes zoster, mumps, hepatitis A, and influenza A virus infections (1, 6, 18, 21). In this paper, we reported that IgA antibodies appearing in serum during infections of the mucosal surfaces by invasive bacteria were also mainly polymeric. In addition, our data clearly indicated the short persistence of polymeric IgA antibodies as compared with monomeric IgA antibodies and demonstrated that in contrast to the results with patients with acute enteritis, the bulk of anti-*C. jejuni* IgA detected in seropositive controls was monomeric. Finally, they confirmed earlier studies indicating that the serum IgA response to antigen delivered through the mucosal route was predominantly IgA1, even in the polymeric fraction of antigen-specific IgA (6, 7).

Extensive absorption experiments demonstrated that the high incidence of anti-*C. jejuni* IgA in the sera of healthy controls was not the result of cross-reactivity with other pathogens or saprophytes of the intestinal tract. It might, however, reflect exposure to cross-reacting antigens. Alternatively, the increased incidence of serum anti-*C. jejuni* IgA with age in controls might suggest that there is continued exposure to *C. jejuni* throughout life. Specific serum IgA might represent a marker for lifetime exposure to *C. jejuni* as already suggested by Blaser et al. (5) while studying immune responses to *C. jejuni* in relation to age in a rural community in Thailand.

The true polymeric nature of IgA antibodies detected during acute enteritis was demonstrated by ultracentrifugation studies at an acid pH, ruling out the presence of circulating IgA immune complexes. The polymeric form of these antibodies might suggest that they were produced in secretory tissues (16) and escaped the transport process operational in secretory glands. The origin of serum IgA remains controversial, but it has been suggested that circulating monomeric IgA or IgA1 antibodies or both are derived mainly from bone marrow, whereas polymeric IgA or IgA2 antibodies or both in serum are derived from mucosal IgA production (2). However, we have previously shown that a parenteral vaccination with tetanus toxoid induces the appearance of polymeric IgA antibodies in serum (F. Mascart-

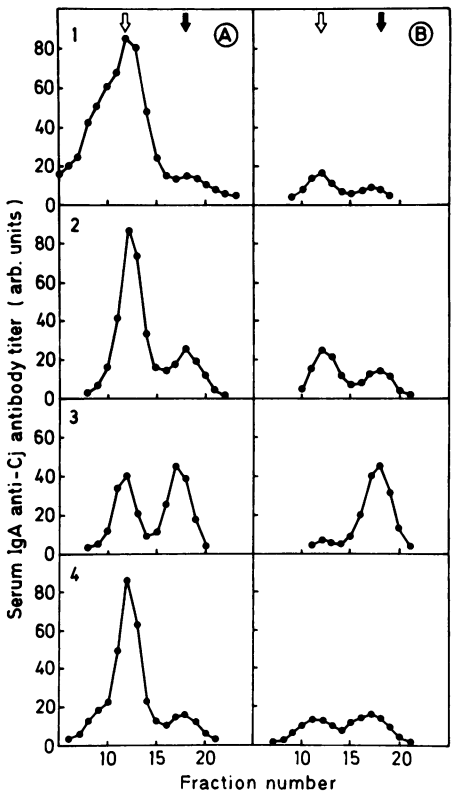


FIG. 5. Molecular size profile of serum anti-*C. jejuni* (Cj) IgA antibodies in four patients at 4 to 15 days (A) and at 25 to 30 days (B) after the onset of acute *C. jejuni* infection (case 1, septicemia [patient 6 in Fig. 4]; cases 2 to 4, enteritis [patients 13, 17, and 14 in Fig. 4, respectively]). Open arrow, Sedimentation position of 10.2S dimeric IgA. Solid arrow, Sedimentation position of 7S monomeric IgA. arb. units = AU.

Lemone, J. Duchateau, M. E. Conley, and D. Delacroix, Immunology, in press). It remains possible, therefore, that invasive *C. jejuni* could stimulate the production of polymeric IgA even in tissues which are known to produce predominantly monomeric IgA.

This study further analyzed the kinetics of polymeric and monomeric IgA antibody responses. Polymeric IgA antibodies appeared more quickly than IgG antibodies and were shorter-lived than both IgG and monomeric IgA antibodies. Monomeric IgA antibodies were detected at low levels at the beginning of the polymeric IgA response, and they remained at about the same titer 1 month after acute infection, probably representing the only detectable specific IgA present later in some patients. The short persistence of polymeric anti-*C. jejuni* IgA than of monomeric anti-*C. jejuni* IgA cannot be explained by the more rapid plasma clearance of polymeric IgA than of monomeric IgA, since the difference in the plasma half-lives of monomeric IgA and polymeric IgA in humans is only about 2 days (12).

The kinetics of quickly rising and falling polymeric IgA antibodies during acute *C. jejuni* infections suggest that polymeric IgA antibodies are linked to a strong or persistent antigenic stimulation or both. A decrease in the polymeric IgA antibody titer would parallel the disappearance of the antigen. In contrast to the polymeric IgA antibody response, no monomeric IgA antibody response could be demonstrated with certitude. During infection, monomeric IgA antibody titers remained low and unchanged, and it was obviously impossible to analyze samples from infected patients prior to infection to demonstrate a seroconversion. It is possible that infection did not stimulate monomeric IgA at all and that monomeric anti-*C. jejuni* IgA could be preexistent to enteritis, as seen in healthy controls.

Finally, the difference in the molecular sizes of anti-*C. jejuni* IgA observed early in infected patients and in seropositive healthy controls represents a potential useful tool for the serological diagnosis of acute infections. The classical problems of the long persistence of antibodies after acute infections and of the high incidence of antibodies in healthy individuals (22) might be overcome with polymeric IgA determination. However, the techniques used to measure separately monomeric and polymeric IgA antibodies first have to be made simpler and more widely applicable.

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