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Serum Immunoglobulin G Analysis to Establish a Delayed Diagnosis of Chronic Cough due to *Bordetella pertussis*

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Abstract

Objectives—Incidence of *Bordetella pertussis* infection among adults has risen significantly throughout the United States, but pertussis is not often considered in the differential diagnosis of chronic cough in adults. The authors hypothesized that serum IgG testing can establish a diagnosis of pertussis infection late in disease presentation when cultures and polymerase chain reaction (PCR) testing are not reliable.

Study Design—Case series with chart review.

Setting—Tertiary care hospital.

Subjects and Methods—Institutional *B pertussis* serum IgG and PCR tests were reviewed since 2007. Clinical factors assessed included vaccination history, duration and severity of cough, and general medical history.

Results—Forty-eight patients had *B pertussis* fimbrial agglutinin IgG levels tested since 2007, with a significant increase in positive IgG tests (>27 IU/mL, 3 times the upper limit of normal) since fall 2009. Nineteen patients (39.5%) met IgG criteria for likely recent pertussis infection. Six IgG-positive patients also had PCR swab testing performed, with 50% positive for *B pertussis*. IgG values were similar for patients with positive or negative *B pertussis* PCR testing with positive IgG titers. IgG-positive patients were much more likely to have posttussive syncope.

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Author Contributions

Jonathan M. Bock, conception and design, data acquisition, analysis, drafting of article, final approval; **Charles C. Burtis**, acquisition of data, drafting of article, final approval; **David M. Poetker**, conception and design, revision of article, final approval; **Joel H. Blumin**, conception and design, revision of article, final approval; **Michael O. Frank**, conception and design, data analysis, revision of article, final approval.

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Recent vaccination for pertussis within the 3 years prior to IgG testing did not significantly increase IgG levels.

Conclusions—One-time *B pertussis* serum IgG testing and patient history can establish a likely diagnosis of recent pertussis infection in the adult patient with chronic cough late in disease presentation when PCR testing is often negative. Pertussis should be considered in the differential diagnosis of all patients with chronic cough.

Keywords

chronic cough; *Bordetella pertussis*; IgG; PCR; diagnosis; syncope

Chronic cough is a common cause of referral to an otolaryngologist and can be a challenging clinical entity to evaluate and treat. Chronic cough is defined as any cough lasting more than 8 weeks.¹ The differential diagnosis of chronic cough is wide and includes such etiologies as gastroesophageal reflux, laryngopharyngeal reflux, laryngeal sensory neuropathy, allergic rhinitis, asthma, and medication side effects.² Pertussis, or whooping cough, is an overlooked and underappreciated cause of chronic cough in adults.³ Pertussis is caused by infection with the fastidious gram-negative bacterium *Bordetella pertussis* and is highly contagious. It is estimated that there are 30 to 50 million cases of pertussis worldwide every year, leading to more than 300,000 deaths. More than 17,000 cases of pertussis were reported in the United States in 2009, but this figure may grossly underestimate the total disease burden because of underreporting.⁴ Large outbreaks of pertussis were seen across the United States in 2010 in adults and infants, with more than 9400 cases and 10 infant deaths reported in California alone.^{4,5} Studies have shown that 10% to 30% of ambulatory patients with chronic cough have evidence of recent pertussis infection after appropriate testing.^{6,7} Although pertussis immunization has been standard in the United States since the 1940s, there continues to be a lack of adequate herd immunity to *B pertussis* in many communities.⁸ Immunity after vaccination wanes over time, leading to recent recommendations for pertussis vaccine booster administrations in adults and health care workers.⁹

Patients with pertussis initially develop a catarrhal infection similar to a mild upper respiratory infection followed by the development of severe coughing paroxysms weeks later.¹⁰ Once coughing develops, it can be present for many months and will not decrease with antibiotic therapy, leading to the appropriate moniker of the postpertussis “one-hundred day cough.”¹¹ It is for this reason that a person with recent pertussis infection may present for evaluation for persistent coughing spells months after initial infection.

Many practitioners are not proficient in evaluating or diagnosing pertussis infection in adults despite the relative prevalence of this disease in the modern world. Adult patients rarely present with the classic “whooping”-type cough for which this disease is known, further making a diagnosis elusive. Adults may complain of severe coughing paroxysms that worsen at night and can be accompanied by posttussive emesis and syncope.¹² Nasopharyngeal cultures and enzyme-linked immunosorbent assays (ELISAs) for *B pertussis* antigens are able to detect an infection for several weeks after the initial catarrhal stage of infection, whereas polymerase chain reaction (PCR) amplification of *B pertussis* DNA may be able to identify bacterial presence for up to a month after initial infection.¹³ Patients will often present to the otolaryngologist for evaluation many weeks after the initial development of coughing paroxysms, which obviates the utility of nasopharyngeal PCR or culture. In this scenario, serum *B pertussis* immunoglobulin G (IgG) testing can be useful as IgG levels remain elevated for years after initial infection.¹⁴ There are no standard parameters for interpreting this test to retroactively establish a diagnosis of pertussis, which

complicates analysis of these values.¹⁵ History of vaccination to pertussis may also elevate serum IgG levels, although the extent and duration of elevation are not clearly known.¹⁶

Several recent patients presented to our clinic with history and examination findings worrisome for pertussis, and timing of their presentation obviated the use of PCR or cultures to establish a diagnosis. On the basis of our experience with these patients, we hypothesized that serologic IgG testing for pertussis is adequate to establish a delayed diagnosis of likely pertussis in patients with chronic cough. We therefore reviewed our institutional experience with the use of serum pertussis IgG testing over the previous 5 years to explore this hypothesis.

Materials and Methods

Patient Selection

The institutional review board of the Medical College of Wisconsin approved this study. All patients with testing of serum IgG levels for *B pertussis* fimbrial agglutinogens (Laboratory Corporation of America, Burlington, North Carolina) during the 4-year window between 2007 and 2011 were identified from both inpatient and ambulatory settings. A retrospective chart review was performed and patient clinical history was reviewed, including history of nasopharyngeal cultures, sputum cultures, pertussis PCR testing, vaccination history (if available), cough duration, severity (posttussive emesis and/or syncope), chest X-ray (CXR), chest computed tomography (CT), chronic obstructive pulmonary disease (COPD), and current medications.

Statistics

Data are presented as mean values with standard deviation. Data were subjected to either a Student *t* test or Fisher exact test to determine statistical significance between groups. Statistical significance for comparison between groups was established at $P < .05$.

Results

Forty-eight adult patients were identified with serum pertussis IgG testing from 2007 to 2011 at the Medical College of Wisconsin. Data from these patients are summarized in Table 1. There were 17 men and 31 women in the group. Average patient age was 52 years, with a range from 20 to 88 years old. Patients were divided into 2 groups based on IgG level and were considered positive for likely pertussis infection based on IgG elevation over 27 IU/mL. This is 3 times the upper limit of normal for this laboratory test and has been shown in a previously published patient series to have 97% sensitivity and 89% specificity for pertussis infection.¹⁷ There were no statistically significant differences in age or sex between divided groups. A summary of IgG values for all 48 patients over time is presented in Figure 1. Nineteen of the 48 patients met criteria for recent pertussis infection based on serum pertussis IgG elevation greater than 27 IU/mL. Eighteen of these positive values occurred since the fall of 2009. Sixteen patients fell in the intermediate group with IgG levels between 9 and 27 IU/mL. Only 13 of 48 patients had IgG levels below 9 IU/mL, considered the upper limit of normal for this laboratory test.

Average pertussis IgG level for the positive and negative groups was 56.1 ± 21.5 IU/mL and 11.3 ± 5.8 IU/mL, respectively. This difference was statistically significant. Pertussis PCR testing was performed in 18 total patients (38%), 12 in the negative group and 6 in the positive group. No pertussis PCR tests were positive in the negative IgG group, whereas 3 of 6 (50%) PCR tests among IgG-positive patients were positive. Cough duration demonstrated a trend toward a shorter course in the positive IgG group, but this was not statistically

significant. There were equal amounts of patients complaining of posttussive emesis in both groups, whereas posttussive syncope was significantly more common among the positive IgG group. IgG-positive patients were also significantly less likely to have a history of COPD. There were more patients tested in the inpatient setting among the IgG-negative group, and these patients were less likely to have CT scans or CXR done to evaluate their cough, but none of these parameters met statistical significance. Notably, only 63.1% of positive patients and 58.6% of negative patients were screened with a CXR for their cough symptoms.

Subgroup analysis was performed for IgG level and cough duration comparing PCR-positive and PCR-negative patients within the IgG-positive group. Average IgG level for IgG-positive, PCR-positive patients was 65.6 ± 23.6 IU/mL ($n = 3$). Average IgG level for IgG-positive, PCR-negative patients was 60.0 ± 30.8 IU/mL ($n = 3$). Average IgG level for IgG-negative, PCR-negative patients was 14 ± 3.8 IU/mL ($n = 12$). There were no patients with negative IgG levels and positive PCR testing. IgG level analysis between IgG-positive patients did not show significant trends relating to PCR testing (either positive or negative), whereas both IgG-positive PCR subgroups had significantly elevated IgG levels when compared with IgG-negative patients. Differences in cough duration between PCR-positive and PCR-negative groups were also analyzed. IgG-positive patients with positive PCR testing had an average cough duration of 5.0 ± 1.0 weeks, compared with 8.7 ± 2.3 weeks for IgG-positive PCR-negative patients. This trend was not statistically significant.

Vaccination history for pertussis was available only for 13 of 48 (27%) patients, including 6 patients from the IgG-positive group and 7 from the IgG-negative group. Patients with confirmed vaccination history were divided into the recent immunization group if their immunization had occurred in the previous 3 years to their serum pertussis IgG test and into the remote group if immunization occurred prior to 3 years previous (Table 2). Mean IgG levels for IgG-positive patients were 81.7 ± 14.6 IU/mL with recent immunization and 71.3 ± 30.0 IU/mL with remote immunization. Mean IgG levels for IgG-negative patients were 15.0 ± 2.9 IU/mL with recent immunization and 13.3 ± 5.6 IU/mL with remote immunization. Analysis for differences between recent and remote immunization status effect on serum pertussis IgG level did not meet statistical significance for either IgG-positive or IgG-negative patient populations.

Discussion

Pertussis is an underappreciated cause of chronic cough in adults, and establishing this diagnosis late in the disease process can be challenging. Heightened clinical suspicion is crucial to detect the patient that may have been infected. Patients who present for evaluation of chronic cough will be beyond 3 to 4 weeks postinfection, when nasopharyngeal cultures and PCR testing are effective. Serum *B pertussis* antigen IgG elevation is the only good option for establishing a likely diagnosis of recent pertussis as the etiologic cause of chronic cough in this scenario. Few guidelines exist regarding interpretation of these values, however. We have reviewed our institutional experience with serum pertussis IgG testing to better understand how this laboratory test can be used to assist in retrospective diagnosis. Mertens et al¹⁷ have previously published their analysis of the utility of serum pertussis one-time IgG and IgA testing in a patient series of 99 adults with culture-confirmed pertussis. They demonstrated that a serum pertussis IgG level over 27 IU/mL was 97% sensitive and 89% specific in diagnosing pertussis infection. When we applied these criteria to laboratory data at our institution, we identified a 39.5% rate of positive pertussis IgG serology among patients with chronic cough who were tested. We have therefore used this amount of IgG elevation as a threshold for likely recent pertussis infection in our patients with chronic cough. For patients with IgG elevation above this level and clinical symptoms consistent

with pertussis (prodromal upper respiratory tract infection, posttussive syncope, inspiratory whoop), no further workup or testing may be needed when other causes of cough have been ruled out. Once diagnosed, treatment of chronic cough related to pertussis is symptomatic. Antitussive medications are typically prescribed, and the patient is informed that the coughing paroxysms will gradually improve over several months. Determination of a diagnosis of pertussis in these patients is of great clinical importance as it offers the patients significant reassurance that their symptoms will get better with time. It can also prevent unnecessary, expensive, and dangerous interventions for patients who require nothing more than supportive care and tincture of time to resolve their coughing.

Serum IgG testing for *B pertussis* antigens is not as specific for establishing a diagnosis of pertussis as nasopharyngeal culture and/or PCR testing, and it should be made clear to the patient that elevated IgG levels can only convey a high likelihood that an infection has occurred. Secondary testing of IgG levels 6 to 12 months later to show a decreasing trend in IgG levels may help reinforce the likelihood of this diagnosis¹⁸; however, no patients in our series had secondary IgG levels drawn to evaluate this concept. IgG levels will remain elevated for many months after infection, making this test the most useful in delayed diagnosis.¹⁶ Testing of pertussis antigen IgM and IgA levels may enhance the sensitivity and specificity of diagnosis but are also only useful in the earlier phases of infection and may not add significantly to diagnostic confidence.¹⁵ Timing of the initial infection is also troublesome because of the time lapse between catarrhal infection and development of the paroxysmal coughing classically associated with pertussis. Mertens et al¹⁷ did assess the ability of IgA elevation to diagnose pertussis infection in their study and found that IgA elevation over 24 IU/mL 4 weeks after infection had a similar 97% sensitivity to diagnose pertussis infection, whereas specificity was only 82% (compared to 89% for IgG elevation). Elevation of serum pertussis IgA levels would certainly suggest recent mucosal immunity to pertussis and a higher likelihood of infection, as IgA levels are not typically induced by immunization to pertussis. However, single-sample IgG testing has been shown previously to have acceptable sensitivity and specificity to establish a likely diagnosis.¹⁹ For this reason, we do not recommend routine assessment of IgA and IgM levels after the acute phase of the likely infection based on patient history.

Our data also define a population of patients with chronic cough and slightly elevated serum pertussis IgG levels between 9 and 27 IU/mL. This level of IgG elevation appears to be consistent with background immunity after vaccination or remote previous infection in our patient population. Just 27% of patients in this series had an IgG level below 9 IU/mL, considered the upper end of normal for this laboratory test. Only 1 patient had no evidence of IgG presence at all, and it is unclear whether this patient had a history of immunization. Vaccination can certainly induce pertussis IgG levels to rise, and interpretation of serum pertussis IgG levels in the time period after vaccination is therefore highly challenging. Dalby et al demonstrated that the half-life of antipertussis toxin IgG decay after vaccination with an acellular booster vaccine was 508 days, whereas the half life after confirmed infection was much shorter, just 221 days.¹⁶ With this as a guideline, it would then seem that elevation of pertussis IgG levels within 3 to 4 years after vaccination or booster administration may be attributable to vaccination. Use of IgG levels to diagnose pertussis is therefore debatable in this time period after vaccination. Our data demonstrate that recent immunization for pertussis did not appear to induce a statistically significant IgG elevation to pertussis fimbrial agglutinogens in the IgG-negative patient group with recent immunization (Table 2), and we would argue that recent immunization status may not interfere with pertussis fimbrial agglutigen IgG interpretation. The emergence of highly virulent strains of pertussis in recent years also makes infection possible even after recent vaccination,²⁰ and in this scenario, clinical history as well as traditional culture or PCR may be the only modalities available to diagnose pertussis. Patients without a history of recent

vaccination with IgG values in this borderline range may still have been infected, and it is suggested that a repeat IgG level may be drawn 6 months later to show a declining trend to further enhance test specificity.

The majority (60.5%) of patients in this series with chronic cough did not have evidence of likely recent pertussis infection. Further workup of cough in these patients can include multiple different modalities.² Reflux can be thoroughly evaluated by 24-hour pH probe testing and esophageal manometry. Pulmonary referral and CXR should be considered in all patients with chronic cough. A significant number of patients in this group may have a sensory neuropathy of the larynx,²¹ and specialized testing for superior laryngeal nerve functional changes by electromyography can assist in this diagnosis.²² Allergy testing and home environmental analysis can also be of use for patients with recalcitrant cough.¹

This patient series suggests several pertinent clinical history factors that raise the possibility of pertussis infection as the cause of chronic cough in the adult population. Posttussive syncope was highly associated with likely pertussis in this group, and other studies have also confirmed the utility of this clinical factor in establishing a diagnosis of pertussis.¹² Patients with COPD were statistically less likely to have positive pertussis serology in this patient series. A shorter overall duration of cough (<3 months) also may suggest a higher likelihood of an infectious etiology. PCR and ELISA for *B pertussis* should be considered when appropriate, as they remain the gold standard for diagnosis of this disease. However, use of these described clinical factors when reviewing patient history may support the utilization of pertussis IgG testing in the evaluation of the patient with chronic cough.

Conclusions

B pertussis is an underappreciated cause of chronic cough in the immunized ambulatory adult population. PCR and ELISA testing, which are the gold standard for *B pertussis* infection, are often negative in this patient group if infection began more than 4 weeks prior to presentation. Patient history and serum pertussis IgG testing can assist in establishing a diagnosis of pertussis in these patients and direct appropriate supportive care and reassurance.

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Figure 1.

Institutional serum *Bordetella pertussis* IgG levels, 2007 to 2011. Solid line = reference normal upper limit for serum *B pertussis* IgG level (9 IU/mL). Dashed line = suggested serum *B pertussis* IgG threshold (>27 IU/mL) consistent with likely recent pertussis infection. IU, international units.

Table 1

Patient Clinical Data Summary

	Serum Pertussis	
	IgG <27 IU/mL	IgG >27 IU/mL
Number (N = 48)	29	19
Sex, % male	34.5	36.8
Age, y	50.9	53.8
Pertussis IgG, IU/mL, mean $\pm$ SD	11.3 $\pm$ 5.8	56.1 $\pm$ 21.5*
PCR positivity, % (number of total tests)	0 (12)	50 (6)*
Cough duration, wk, mean $\pm$ SD	16.4 $\pm$ 4.5	10.3 $\pm$ 3.9
Posttussive emesis, %	24.1	26.3
Posttussive syncope, %	17.2	47.3*
History of COPD, %	27.6	5.3*
% Tests as inpatient	37.9	21.1
CT scan performed, %	31.0	47.4
CXR performed, %	58.6	63.1

Data are presented as either mean with standard deviation or percentage of cases with observed finding. Abbreviations: COPD, chronic obstructive pulmonary disease; CXR, chest X-ray; IgG, immunoglobulin G.

* $P < .05$.

Table 2

Comparison of Serum Pertussis IgG Values in Patients with Confirmed Vaccination History

	Remote Vaccination	
	>3 y	<3 y
IgG+ (>27 IU/mL, n = 6)	71.3 ± 30 (n = 3)	81.7 ± 14.6 (n = 3)
IgG- (<27 IU/mL, n = 7)	13.3 ± 5.6 (n = 3)	15.0 ± 2.9 (n = 4)

Data are presented as mean value with standard deviation. Abbreviations: IgG, immunoglobulin G; IU, international units.