Editorial

Pertussis: A Continuing Hazard for Healthcare Facilities

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In 1999, 7,288 cases of pertussis were reported to the Centers for Disease Control and Prevention (CDC).[1] High rates of pertussis, compared with other pediatric vaccine-preventable diseases, continued to occur even though, since 1995, the coverage rate with at least three doses of a pertussis-containing vaccine has been greater than 95% among US children aged 19 to 35 months.[2]

The continuing high rates of pertussis in the United States pose a challenge for infection control professionals to develop new strategies to recognize and manage nosocomial outbreaks of pertussis. In this issue, Martinez and colleagues describe a hospitalwide outbreak of a *Bordetella pertussis*-like illness and report that the use of postexposure prophylaxis with azithromycin was tolerated well and resulted in few healthcare workers (HCWs) missing work.[3]

CHANGING EPIDEMIOLOGY OF PERTUSSIS: IMPORTANCE OF INFECTION IN ADULTS

Since 1980, the number of reported cases of pertussis has increased in the United States. Possible reasons for this rise could include increased awareness of pertussis among healthcare providers, increased use of more sensitive diagnostic tests, and better reporting of cases to health departments.[1] Because vaccine-induced immunity wanes within 5 to 10 years after pertussis vaccination, most adolescents and adults are susceptible to disease.[4,5] In contrast to the period 1990 through 1993, during 1994 through 1996, the incidence of pertussis reported to the CDC among preschool-aged children did not change, but the incidence among adolescents aged 10 to 19 years and adults increased by more than 90%.[6] An analysis of surveillance data from 1989 to 1998 in Massachusetts also noted that the incidence in children remained stable, whereas the incidence in adolescents and adults increased; indeed, by 1998, 92% of cases occurred in adolescents and adults.[7]

Pertussis is increasingly recognized as a case of chronic cough in adults.[8-11] Serological studies of prolonged cough illnesses in US adolescents and adults indicated that between 12% and 26% result from *B pertussis* infection.[12-15] Studies in other developed countries have produced similar results.[11] The varying incidence rates reported depend, in part, on differences in study populations (eg, age), clinical definitions of disease (eg, duration of cough), and laboratory criteria for diagnosis.[16]

Pertussis in young children remains a serious disease. Common complications include pneumonia, 9.4%; seizures, 2.3%; and encephalopathy, 0.5%. Death occurred in 0.9% of children, all under 6 months of age.[17] Adults with pertussis frequently experience prolonged cough, sleep disturbed by cough, and cough followed by choking or vomiting.[18] Complications have been reported to be more common in adults than adolescents (28% vs 16%), with pneumonia occurring in 5% to 9% of persons older than 30 years of age.[19] Subclinical pertussis may be common in adults with household exposure.[20]

Adolescents and young adults play an important role in the transmission of pertussis, because immunization-induced immunity to pertussis wanes with increasing age, and because disease in adults frequently is not diagnosed or treated, as it often is atypical or mild.[21]

LESSONS FROM NOSOCOMIAL OUTBREAKS

Only limited data are available regarding the frequency of nosocomial exposures or outbreaks due to pertussis. Haiduven and colleagues reported that, between

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01-ED-192. Weber DJ, Rutala WA. Pertussis: a continuing hazard for healthcare facilities. Infect Control Hosp Epidemiol *2001;22:736-740.*

1989 and 1997, their medical center had 49 pertussis exposures that originated in pediatric units or clinics.[22] Our experience is similar: 74 employees were exposed to 25 patients with pertussis between 1994 and 1998.[23] We found pertussis to be the third most common disease resulting in HCW exposure, following only varicella-zoster and tuberculosis. Wright and colleagues assessed the incidence of pertussis infection in two cohorts of HCWs, based on serology, and reported annual incidence rates of 1.3% and 3.6% among residents and emergency department staff, respectively.[24] Some employees had clinically unrecognized cases, whereas others had a history of a prolonged cough illness.

Multiple outbreaks of pertussis in healthcare facilities have been reported in the literature.[25-35] These outbreaks have resulted from failure to recognize and isolate infected infants and children, failure to recognize and treat disease in staff members, and failure to institute control measures rapidly. Nosocomial acquisition of pertussis by HCWs has occurred during several outbreaks.[26-28,32-35]

Recommendations and protocols for the management of pertussis in healthcare facilities, including isolation, postexposure prophylaxis of patients and HCWs, and management of infected workers, have been published by the CDC[36] and infectious disease experts[22,37] and include the following: (1) isolate suspected or known infected patients using Droplet Precautions; (2) provide postexposure prophylaxis for all asymptomatic exposed employees; (3) evaluate all symptomatic employees for pertussis, and provide appropriate therapy; and (4) furlough symptomatic employees during the first 5 days of their therapy. The rationale for recommending Droplet Precautions for at least 5 days following the initiation of effective therapy has been strengthened by a study that detected *B pertussis* DNA as far away as 4 m from the patient's bedside for up to 4 days following initiation of therapy.[38]

Recent advances that will have an impact on the management of pertussis in the hospital include the availability of new diagnostic tests, data demonstrating efficacy and safety of acellular pertussis vaccines in adults, and both in vitro and clinical data demonstrating efficacy of the newer macrolides (clarithromycin and azithromycin) for the therapy of pertussis.

NEW DIAGNOSTIC TESTS

The diagnosis of pertussis remains clinically challenging. Culture remains the "gold standard" but has poor sensitivity. The sensitivity of culture is affected by the disease stage, collection method, collection device, transport time and media, and incubation conditions.[39] The ability to isolate pertussis decreases rapidly after the paroxysmal stage begins. Nasopharyngeal aspirates improve the yield compared to nasopharyngeal swabs. The preferred culture medium is charcoal agar supplemented with 10% horse blood and cephalexin (Regan-Lowe medium).

Direct fluorescent antibody testing on nasopharyngeal secretions has been used for rapid diagnosis, but this method suffers from low sensitivity (compared with culture) and low specificity.[39,40]

Serological methods have been used widely in clinical research but have limited application for clinical diagnosis or management.[11] Enzyme-linked immunosorbent assay (ELISA) is the method of choice for *B pertussis* serology.[41] Compared with reference ELISA tests, commercial ELISA kits may yield false-positive or -negative results and need further improvement.[42]

Assays using the polymerase chain reaction (PCR) are rapidly becoming the diagnostic method of choice.[11] Compared with culture, PCR has improved sensitivity while retaining excellent specificity.[43,44] Because there have been few comparative studies on DNA-preparation methods and PCR assays, there currently is no consensus regarding which PCR assay is the best.

ACELLULAR PERTUSSIS VACCINE IN ADULTS

Acellular pertussis vaccines have been demonstrated to have similar or improved efficacy compared to the whole-cell pertussis vaccine, with a lower frequency of febrile reactions.[45-50] For this reason, only acellular pertussis vaccine is recommended in the current childhood immunization schedule in the United States.[51] Reactogenicity of the whole-cell vaccine has long limited its use to children less than 7 years of age. Although whole-cell vaccine has been used successfully in conjunction with erythromycin prophylaxis to control a nosocomial outbreak, local reactions were common, and two adult vaccines developed systemic symptoms.[27] In randomized, placebo-controlled trials, acellular pertussis vaccines have been shown to be both safe and highly immunogenic in adolescents and adults.[52-57] Based on these studies, the targeted use of acellular pertussis vaccine in adolescents and adults at risk of pertussis, including HCWs, has been recommended.[58-60] Immunization of HCWs with acellular pertussis vaccine has been used along with chemoprophylaxis to control nosocomial outbreaks.[61,62] It is likely that, in the future, acellular pertussis vaccine will be recommended for HCWs, either routinely or as an intervention during an outbreak.[63]

In several countries where whole-cell vaccine has been used, there is evidence that the incidence of pertussis is increasing despite high vaccine coverage. Sequence analysis of strains from both European countries and the United States has revealed polymorphism in the amino acid sequence of pertactin (prn) and the pertussis toxin (PT)-S1 subunit.[64-67] Nonvaccine genotypes of both prn and PT-S1 have gradually replaced the vaccine types in these countries. Evidence has suggested that whole-cell vaccine provides better protection against strains with the vaccine type prn than against strains with nonvaccine prn types.[64] However, the exact role played by these genetically distinct strains in the resurgence of pertussis remains to be elucidated.[68] Rapid methods for identifying *B pertussis* prn-gene variants have been described.[69]

THERAPY FOR PERTUSSIS, INCLUDING POSTEXPOSURE PROPHYLAXIS

Erythromycin is the only drug approved by the Food and Drug Administration for the treatment of pertussis; the estolate form is preferred by some clinicians because of superior pharmacokinetics. *B pertussis* is highly susceptible in vitro to erythromycin.[70-72] Erythromycin has been shown to decrease the duration of illness when administered early in the course of pertussis and to eliminate *B pertussis* from the nasopharynx. For these reasons, erythromycin is considered the drug of choice for the treatment and prophylaxis of pertussis.[72-76]

Erythromycin therapy of index cases in the community has been used successfully to reduce secondary cases of pertussis in households.[77,78] Although chemoprophylaxis of exposed household members has been recommended, based on uncontrolled studies, a randomized placebo-controlled trial of erythromycin chemoprophylaxis for household contacts of children with culture-positive *B pertussis* failed to demonstrate a reduction in clinical pertussis.[79] Therapy of infected patients and chemoprophylaxis of exposed HCWs has been successful in terminating outbreaks in healthcare institutions.[27,80] The potential epidemiological flaws in clinical trials of erythromycin prophylaxis have been reviewed.[81]

Erythromycin-resistant clinical isolates of *B pertussis* have been reported, raising concern about the use of macrolides for therapy or prophylaxis[82,83]; however, recent surveys of *B pertussis* strains demonstrate that macrolide resistance is uncommon.[70-72] *B pertussis* is susceptible in vitro to trimethoprim-sulfamethoxazole,[71,72] the newer macrolides azithromycin and clarithromcyin,[70,72] and the quinolones levofloxacin, ciprofloxacin, ofloxacin, and gatifloxacin.[72] Trimethoprim-sulfamethoxazole has been demonstrated to be effective in small clinical trials[84] and therefore is the recommended alternative for treatment or prophylaxis of individuals intolerant to erythromycin[73,76]; however, its efficacy as a chemoprophylactic agent has not been evaluated. Small clinical trials suggest that clarithromycin and azithromycin also are effective for the treatment of pertussis.[85] Although older studies had suggested that a 14-day course of erythromycin therapy was required from eradication of *B pertussis,* recent trials have suggested that the following shorter courses of antibiotics are as successful as the standard 14-day course of erythromycin: 7 days of erythromycin esolate (40 mg/kg/d; maximum dose 1 g),[86] 7 days of clarithromycin,[85] or 5 days of azithromycin.[85] In this issue, Martinez and coworkers provide evidence that azithromycin was tolerated well by HCWs.[3] Because of the high frequency of gastrointestinal intolerance with erythromycin, we also have switched to one of the newer macrolides (ie, azithromycin or clarithromycin).

CONCLUSION

Despite high rates of pediatric vaccine coverage, pertussis continues to be an important childhood disease. Pertussis is now recognized as a common cause of prolonged cough in adults. Multiple hospital outbreaks have been described. Recognition of infection in patients may be facilitated by diagnostic testing using PCR. The drugs of choice for chemoprophylaxis at the current time are azithromycin or clarithromycin. The use of acellular pertussis vaccine for HCWs is likely to be recommended in the near future, either routinely or in outbreak settings.

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