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Pertussis

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CASE PRESENTATION\textsuperscript{1}

A 19-day-old female infant was admitted to a neonatal ICU in Ankara, Turkey. A product of an unremarkable gestation and vaginal delivery at 39 weeks, she began to have symptoms of an upper respiratory infection at the age of 15 days. The illness abruptly worsened 3 days later with cough, cyanosis, periods of apnea, and progressive respiratory failure precipitating her admission. The mother, who had received DPT (diphtheria, pertussis, and tetanus) vaccination as a child, reported a mild cough beginning in the 2 weeks prior to delivery. Upon arrival, the infant was having apneic episodes with cyanosis and her $O_2$ saturation dropped to 36% during a coughing spasm. An initial white blood cell count was 27,200/µL with 60% lymphocytes and a chest X-ray did not reveal any infiltrates.

Despite ampicillin and gentamicin, she deteriorated further and endotracheal intubation was necessary but was discontinued on day 2 of her admission. Nasopharyngeal washings were tested by PCR and were negative for respiratory syncytial virus, influenza A and B, adenovirus, parainfluenza virus, and coronavirus. Based on the infant’s symptom complex and lymphocytosis, she had erythromycin therapy added on day 4. Nasopharyngeal aspirates obtained before erythromycin treatment was begun were positive for pertussis by PCR and by culture on Bordet–Gengou agar. The infant’s serum antibody against pertussis toxin was undetectable. The infant slowly improved with fewer bouts of paroxysmal coughing and she was discharged on hospital day 10. The mother was the only contact who reported cough and was the only contact that was seropositive for pertussis although her culture was negative.
1. BRIEF JUSTIFICATION ON WHY THIS CASE WAS IDENTIFIED AS EMERGENT

As shown in Figure 27.1 from the Centers for Disease Control and Prevention (CDC) and further discussed in the section on frequency and epidemiology, the numbers of reported cases of pertussis in the USA and other parts of the developed world began to increase from 10,000 to 25,000 in the first decade of the 21st century. In 2012, almost 50,000 cases were reported, the highest number of cases since 1955 with many infected infants requiring hospitalization, including at least 18 deaths. Outbreaks were also occurring in Europe, Australia, and Japan. It is this dramatic increase, which appears to be tied to the introduction of the safer vaccine (the pertussis paradox), that has made this infection an emerging (actually reemerging) disease, which has its highest risk of significant morbidity and mortality in infants.

2. WHAT IS THE CAUSATIVE AGENT?

The primary cause of pertussis, Bordetella pertussis, is one of eight species of the Bordetella genus. Among the group, B. pertussis, B. parapertussis, and B. bronchiseptica are the most studied. B. bronchiseptica causes kennel cough in dogs and asymptomatic carriage can occur in many animals, but is
not a usual human pathogen. The organism appears to be the evolutionary ancestor of both \textit{B. pertussis} and \textit{B. parapertussis}. The organisms are highly trophic for the cilia of the mucosa of the respiratory system and from this location a significant number of toxins are produced, which participate in the disease pathogenesis.

\textit{B. pertussis} is a small, strictly aerobic, Gram-negative coccobacillus that is quite fastidious, requiring specific media for its isolation. The morphology of the organism is not distinguishable from other \textit{Bordetella} or from \textit{Haemophilus} species. \textit{B. pertussis} is non-motile, oxidase positive, catalase positive, and is relatively inert biochemically. The organism is only isolated from humans.

3. WHAT IS THE FREQUENCY OF THE DISEASE?

Pertussis (whooping cough) remains the most commonly reported vaccine-preventable disease in the United States in children younger than 5 years. Pertussis immunization as part of the DPT vaccine was introduced in the United States in the late 1940s and, as can be seen in Figure 27.1, the number of reported cases dropped slowly over the decades of the 1950s and 1960s (with periodic bumps characteristic of the infection) to a nadir of 1010 cases in 1976. That number is >99\% lower than the number of cases in 1947. The numbers of reported cases remained low but in the 2000—4500 range through the mid-1990s. Because of issues of reactogenicity with DPT related to the whole cell pertussis component, which became a political issue as the vaccine was inaccurately blamed for permanent brain damage among other things, the pertussis pediatric immunization schedule was gradually changed to an acellular one. This vaccine utilizes acellular pertussis toxoids, which were much better tolerated and seemed to produce a similar immune response as compared to DPT. Unlike DPT, the vaccine with a smaller amount of pertussis toxoids (Tdap) could be tolerated in adults.

In 2010, according to CDC, the US pertussis rate reached 27,550 cases (the highest number since 1959), with 27 related deaths.

In 2011, according to statistics from CDC, adolescents (aged 11—19 years) and adults together accounted for 47\% of pertussis cases, while children aged 7—10 years accounted for 18\% of cases.

During 2012, 48,277 cases of pertussis were reported to CDC. The incidence rate of pertussis among infants exceeds that of all other age groups. The second highest rates of disease are observed among children 7—10 years old. Rates also increased in adolescents 13 and 14 years of age. Eighteen pertussis-related deaths during 2012 have been reported to CDC. Almost all of the deaths occurred among infants younger than 3 months of age. During 2012, increased pertussis cases or outbreaks were reported in a majority of states. Forty-nine states and Washington, DC reported increases in disease in 2012 compared with 2011.
CDC has estimated that 5–10% of all cases of pertussis are recognized and reported. In studies, 12–32% of adults with prolonged (1–4-week) cough have been found to have pertussis. It is estimated worldwide to be 48.5 million cases, with a mortality rate of nearly 295,000 deaths per year. The case-fatality rate among infants in low-income countries may be as high as 4%.

4. HOW ARE THE BACTERIA TRANSMITTED?

Pertussis is a highly contagious respiratory infection, particularly in the household setting. Indeed, direct inoculation with as few as 140 organisms can cause disease in susceptible children. In a review, attack rates for unvaccinated children in the household setting ranged from 64 to 86% (average 76%) but was much lower (range 0–36% in classroom contact studies). Clearly, transmission required repeated or prolonged exposure and/or close contact. Airborne transmission via respiratory droplets had been postulated but not clearly proven until 2012 when Merkel’s laboratory demonstrated airborne transmission between infected and naïve baboons.

4.1 Household

Transmission of the infection to high risk infants tends to occur from inside the family unit. An Australian review reported that 39% of the time the mother was the source, 16% fathers, 5% grandparents, and both siblings and non-family sources had very heterogeneous rates. In as many as 52% of circumstances, no source was identified. In a Dutch review, the estimated relative infections of mothers were 3.9 and fathers 0.44. A report from Korea came to similar conclusions. Clearly, the mother appears the major player in neonatal transmission and should be at the head of the line if selective, rather than universal, family “cocooning” of the infant is used. Even an entire family vaccination may miss potential exposures as 37% of contacts of English infants aged <10 weeks were non-household individuals lasting >15 minutes.

4.2 Nosocomial

Perhaps the worst scenario for nosocomial transmission of B. pertussis is a neonatal nursery. In 2003, such an outbreak (prior to the acellular vaccine use) was introduced by a symptomatic nurse who was not diagnosed with the infection despite a characteristic illness. The nurse had made multiple health-care visits but the disease was detected only after a 2-month-old premature infant developed pertussis and four other nurses were subsequently diagnosed with pertussis, probably transmitted by the nurse prior to diagnosis. Azithromycin prophylaxis was recommended to all infants in the unit during the time of the illness of the index nurse. Seventy-two infants received
post-exposure prophylaxis (PEP) as well as 72 healthcare workers (HCW). No other infant cases occurred but a resident physician who cared for the ill infant and declined prophylaxis did develop pertussis. A more recent outbreak among oncology nurses also showed transmission among HCW and none from the HCW to patients.\textsuperscript{11} With the availability of acellular pertussis vaccine boosters, HCW, especially those with exposure to infants, should be vaccinated.

5. WHICH FACTORS ARE INVOLVED IN DISEASE PATHOGENESIS? WHAT ARE THE PATHOGENIC MECHANISMS?

As reviewed by Preston,\textsuperscript{12} de Gouw et al.,\textsuperscript{13} and Hewlett,\textsuperscript{14} \textit{B. pertussis} produces a cadre of factors involved in pathogenesis. The major adhesion factors enabling close contact of the organism and the respiratory epithelium are filamentous hemagglutinin (FHA), fimbriae, and pertactin (prn). Both FHA and prn are included in the antigen profile of the acellular vaccine. The toxins produced by the organism include:

- pertussis toxin (Ptx), a complex hexameric protein that is an ADP-ribosyltransferase;
- adenylate cyclase toxin (ACT), which is post-translationally modified to be able to facilitate apoptosis and cytotoxicity;
- a type 3 secretion system effector protein such as BteA that induces rapid, non-apoptotic cell death; and
- tracheal cytotoxic (TCT), a disaccharide tetrapeptide derived from the organism’s cell wall, which causes ciliostasis and damages respiratory epithelial cells.

Ptx is a major part of the forms of the acellular pertussis vaccine and is felt to play a major role in the disease but it cannot be a \textit{sine qua non} for the disease as \textit{B. parapertussis} can produce a very similar disease despite not producing Ptx. \textit{B. parapertussis} does contain the gene for Ptx but does not express it because of mutations in the promoter gene.

\textit{B. pertussis} contains several regulatory systems controlling the expression of the virulence genes in response to environmental signals; the most notable of these is bvgASR. The organism also contains several iron acquisition systems.

In addition to these varied adherence and toxic factors, the organism can successfully persist in the human host by its ability to “interfere with almost every aspect of the immune system, from the inhibition of complement and phagocyte-mediated killing to the suppression of T- and B-cell responses”.\textsuperscript{13} Further understanding of the immune system modifications facilitated by the organism may assist in developing more effective vaccines.
6. WHAT ARE THE CLINICAL MANIFESTATIONS?

Pertussis generally has an incubation period of 7–10 days but it is important to realize that more than a fifth of secondary cases in a German household milieu presented more than 4 weeks following the primary case onset, which may reflect a longer incubation period or exposure later in the primary case’s illness. As reviewed by Cherry and Heininger and Mattoo and Cherry, there are many factors that impact on the pertussis illness including age and previous immunization status of the individual, size of inoculum, antimicrobial therapy, presence of passively acquired specific antibody, and genetic factors of both the host and the organism.

Pertussis is an acute infection of the respiratory tract and the classical illness most frequently occurs as a primary infection in young, unimmunized children. The clinical course of the 6–12-week process is divided into three stages:

1. The catarrhal phase is characterized by insidious onset of mild upper respiratory symptoms similar to rhinovirus infections including low-grade fever, coryza, sneezing, and a mild, occasional cough. During the 1–2 weeks of this stage, the cough gradually becomes more severe.

2. The paroxysmal phase manifests as spasmodic coughing episodes, or paroxysms of as many as 10 or more coughs without an inspiration. These spasms sometimes are followed by a long inspiratory whooping sound and/or by posttussive vomiting. Paroxysmal attacks occur more frequently at night and may be precipitated by eating. Cyanosis can occur during paroxysms and the spasmodic cough may have many complications including cerebral hypoxia, subcutaneous emphysema, subconjunctival hemorrhage, umbilical or inguinal hernia, rib fracture, severe alkalosis, and seizures. Young children and infants may appear quite distressed and exhausted following an episode. Remarkably, the child can appear well between attacks. This stage usually lasts 2–6 weeks, but may persist for up to 10 weeks. Neither fever nor pharyngitis is common in pertussis unless secondary bacterial superinfections intervene.

3. In the third or convalescent phase, recovery is gradual with paroxysms subsiding initially in frequency and then in severity and the cough may disappear in 2–3 weeks. Paroxysmal episodes may return with other respiratory infections.

It is important to be aware that mild or even asymptomatic infection can occur especially in previously immunized children, adolescents, and adults, but even in unimmunized children, as many of 5% of apparently healthy infants had polymerase chain reaction (PCR) evidence of pertussis. The milder illness in older children, adolescents, and adults is manifest by chronic cough lasting 3–4 weeks or longer. In a report of a group of college students who were not clinically diagnosed with pertussis but found to have
laboratory evidence of the illness,\textsuperscript{19} the mean length of cough was 3 weeks. The only two features differentiating pertussis from non-pertussis in the study were non-productive cough and less likely previous use of antimicrobials. Classical pertussis can occur in adults and it has been observed that adults immunologically primed from previous infection were more likely to have typical pertussis than those primed by immunization.\textsuperscript{17}

Clearly, much of the severe morbidity and almost all of the mortality from \textit{B. pertussis} infection occur in those younger than 6 months. As many as 63\% of infants younger than 6 months of age with pertussis require hospitalization.\textsuperscript{20} In this CDC report from infants with pertussis in 1997–2000, there were 11.8\% with pneumonia, 1.4\% seizures, 0.2\% encephalopathy, and 0.8\% died. This compares with parallel numbers of 28, 8.6, 0.7, 0.1, and <0.1\% in infants 6–11 months of age.

Neonatal pertussis is observed to be especially severe with as much as a 3\% risk of death.\textsuperscript{17} Symptoms can be substantially different with periods of apnea and sometimes hypoxia-induced seizures usually the most common manifestation of infection. The cough is present, but so weak that it may be unrecognized. In these children with so-called malignant pertussis, leukocytosis, particularly with white blood cell (WBC) counts of 30,000 to 100,000, and severe pulmonary hypertension are ominous signs for mortality.\textsuperscript{21} In a study comparing neonatal pertussis to other neonatal respiratory infections,\textsuperscript{22} pertussis-positive neonates had longer hospital stays, less fever, more apnea and cyanosis spells, required more days of supplemental O\textsubscript{2} in the hospital, and represented all the infants discharged on respiratory supportive care.

7. \textbf{HOW DO YOU DIAGNOSE?}

\textbf{Figure 27.2} shows the timing of pertussis diagnostic studies.

Symptom complexes such as a spasmodic cough without fever or chronic cough for more than 3 weeks should suggest the diagnosis of \textit{B. pertussis} infection and appropriate tests should be performed. A video demonstrating

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig27.2}
\caption{The timing of pertussis diagnostic studies. From: CDC.}
\end{figure}
the proper technique of obtaining specimens for culture and PCR can be found at: https://www.youtube.com/watch?v=DVJNWefmHjE&feature=related.

7.1 Culture
Isolation of \textit{B. pertussis} from nasopharyngeal specimens (not pharyngeal) remains the gold standard for diagnosis. Culture is 100\% specific. The degree of sensitivity (12\textendash 60\%) is modified by length of illness, vaccination status, and patient age,\textsuperscript{23} and is highest during the initial catarrhal phase. Isolation requires special transport and culture material such as Bordet\textendash Gengou agar. Positivity can require 3\textendash 7 days of incubation.

7.2 PCR
PCR for \textit{B. pertussis} offers a higher sensitivity than most techniques but there is no standardized testing and may be positive with other \textit{Bordetella} species. Results are obtained within 1 day. The assays are much more sensitive late in disease and can be still positive if only non-viable organisms are present. PCR is a supplement to, not a replacement for, culture.

A direct fluorescent antigen stain is available but is not generally recommended for diagnostic use and serologies are also available. Antibodies against Ptx and filamentous hemagglutinin are also available. Anti-pertussis toxin (anti-Ptx) may take 3 weeks to become detectable and anti-FHA can help distinguish different \textit{Bordetella} species, but neither test is US FDA approved.\textsuperscript{23}

8. HOW DO YOU DIFFERENTIATE THIS DISEASE FROM SIMILAR ENTITIES?
Especially early in pertussis illness, prior to or early in the spasmodic cough, a variety of respiratory viruses such as the rhinovirus, respiratory syncytial virus, parainfluenza virus, adenovirus, and influenza may be confused with pertussis. Specific tests for these agents along with pertussis can help but it needs to be remembered that pertussis can co-infect with a respiratory virus and diagnosing a respiratory virus does not exclude the possibility of pertussis.\textsuperscript{24} Especially in populations currently immunized with the acellular vaccine, mild pertussis can be difficult to differentiate from \textit{B. parapertussis} and other viral or bacterial respiratory infections.\textsuperscript{25}

Infection with \textit{B. parapertussis} can cause a disease similar to pertussis but parapertussis tends to be milder and of shorter duration than pertussis. It appears that in some areas such as Scandinavia, the two infections can be of equal frequency but generally diagnosed less often and the ratio of subclinical to clinical illness is much higher in parapertussis.\textsuperscript{26} In culture, \textit{B. parapertussis}
is less fastidious, is oxidase negative, urea positive, and produces a brown pigment on heart infusion agar. Using different primers for PCR, pertussis (with IS481) and parapertussis (IS1001) can be differentiated, although IS1001 is present in *B. bronchiseptica*. Serologically, parapertussis does not express Ptx so that Ptx antibodies can distinguish the illnesses of pertussis and parapertussis but the antibody responses to FHA and prn are of similar magnitude.

*B. holmesii*, a more recently described organism, had been initially described as a cause of bacteremia but can cause a symptom complex similar to *B. pertussis* and, like *B. parapertussis*, can co-circulate in a population. *B. holmesii* contains IS481 as *B. pertussis* but does not produce an anti-PT response. It appears that current vaccination of adolescents and adults does not affect the incidence of *B. parapertussis* or *B. holmesii* as much as *B. pertussis*.

9. WHAT IS THE THERAPEUTIC APPROACH?

With increasing incidence and widespread community transmission of pertussis, extensive contact tracing and broad-scale use of PEP among contacts may not be an effective use of limited public health resources. While antimicrobial agents may prevent pertussis if given prior to symptom onset, there are no data to indicate that widespread use of PEP among contacts effectively controls or limits the scope of pertussis outbreaks. If used, PEP use should be targeted to persons at high risk of developing severe pertussis and to persons who will have close contact with those at high risk of developing severe pertussis.

A 2007 Cochrane Review looked at 13 trials with 2197 participants: 11 trials investigated treatment and two trials investigated prophylaxis. Short-term macrolide antimicrobial use (azithromycin for 3 to 5 days, or clarithromycin or erythromycin for 7 days) were as effective as long term (erythromycin for 10 to 14 days) in eradicating *B. pertussis* from the nasopharynx and had fewer side effects. Trimethoprim/sulfamethoxazole for 7 days was also effective. There were no differences in clinical outcomes or microbiological relapse between short- and long-term antimicrobial use. Indeed, while therapy is effective in eliminating *B. pertussis* from patients with the disease, rendering them non-infectious, treatment does not alter the subsequent clinical course of the illness. The review also found that contact prophylaxis of contacts older than 6 months of age with antimicrobials did not significantly improve clinical symptoms or the number of cases developing culture-positive *B. pertussis*.

Rarely, *B. pertussis* has been found to be resistant to macrolides. Most of the resistant isolates are reported from the USA but a 2012 report from France also documented resistance.
10. WHAT ARE THE PREVENTIVE AND INFECTION CONTROL MEASURES?

Vaccination has been the primary way of prevention of pertussis. As previously noted, the number of cases of pertussis in the industrialized world has increased in the wake of introduction of the acellular pertussis vaccine (DTaP in primary immunization of children and Tdap in adults). The small letters d and p in the adult vaccine represents a lower amount of immunogen given.

As reviewed by Cherry, the pertussis reemergence may well be related to increased awareness of the disease, changes in case definition, increased incidence of non-pertussis Bordetellae and the greater availability of PCR as a diagnostic test. However, several other issues exist regarding this rise in the incidence of pertussis, including lower potency of DTaP contributing to a more rapidly waning immunity and potential genetic drift of strains of B. pertussis.

Clearly, the current formulation of the acellular pertussis vaccine is less potent than its whole cell ancestor. Whether measuring specific antibodies to proteins in the vaccine during the primary sequence or assessing pertussis incidence after the sequence ends at age 5, immunity to pertussis promptly waned. Indeed, pertussis incidence and risk ratios rose in the three study states to as high as 8.8 times and 3.9 times in Minnesota between year 1 and year 6 after completion of the sequence. Currently, three-antigen and five-antigen component acellular pertussis vaccines are available in the USA. The five component vaccine had greater efficacy in a head-to-head comparison. Interestingly, the relative risk of pertussis was 8.57 times higher in those with a five-dose aP schedule as compared to those who had received at least one dose of whole cell vaccine, while those with six doses of aP had a relative risk of 3.55 as compared to the one or more whole cell group. Whether changing the balance of antigens in the vaccine or adding different antigens is unclear. In a response to the waning immunity observed following the primary immunization sequence of the acellular pertussis vaccine, further immunizations were recommended first for adolescents, then for adults 19–64 years old, and then for adults 65 years and older. Finally, in order to best “cocoon” the as yet unborn baby, recommendations now exist for aP vaccination of the pregnant woman in the 2nd or 3rd trimester.

Evolutional changes have been observed in B. pertussis that may have had a role in the organism’s ability to persist in a highly immunized population. Despite the genetically monomorphic nature of the pathogen without horizontal acquisition of new genes, Mooi and colleagues have observed strains carrying a mutation in the gene for the Ptx gene promoter, which mediates increased production that was associated with pertussis resurgence and other genetic differences between surface proteins including Ptx, prn, and fimbriae. Additionally, Lan’s Australian group have divided
B. pertussis isolates into six clusters based on single nucleotide polymorphisms (SNPs). The reemergence of pertussis seemed to coincide with the emergence of SNP cluster 1 of strains carrying prn and Ptx genes (prn2 and ptxP3) able to evade acellular pertussis vaccine-induced selective pressure.

It is likely that waning immunity related to the acellular pertussis vaccine and selective pressure of this vaccine have worked in tandem with better recognition of the illness to cause this “pertussis paradox”. It may well be the case that a better vaccine may be needed to control this resurgence and better protect the susceptible infant.

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