INTRODUCTION

Malignant pertussis is a rare, life-threatening illness characterized by severe respiratory failure, severe leukocytosis, and pulmonary hypertension, with a high mortality rate. Current therapies include supportive care and leukoreduction. Notably, leukoreduction might be more effective when initiated prior to the development of organ failure and pulmonary hypertension.

KEYWORDS
Bordetella pertussis, hydroxyurea, leukoreduction, malignant pertussis, Saudi Arabia, whooping cough

CASE SERIES

2.1 Case 1

A 10-month-old baby boy born preterm at 29 weeks, with a history of admission in the neonatal intensive care unit for respiratory distress syndrome, neonatal jaundice, and sepsis, was admitted to the King Abdullah Specialized Children Hospital (KASCH), an academic governmental tertiary center in Riyadh, Saudi Arabia. Table 1 shows the patients’ demographics and characteristics, and the treatment provided.

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Leukoreduction and hydroxyurea in malignant pertussis: A case series

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Abstract

We report five cases of malignant pertussis, a rare but life-threatening illness. Current therapies include supportive care and leukoreduction. Notably, leukoreduction might be more effective when initiated prior to the development of organ failure and pulmonary hypertension.

1 INTRODUCTION

The coccobacillus Bordetella pertussis is re-emerging after decades of control, despite being a disease preventable by vaccination. Pertussis is associated with multiple clinical syndromes in infants, including apnea/bradycardia pertussis, pneumonic pertussis, and malignant pertussis. For decades, leukocytosis has been known as a prominent characteristic of pertussis, correlating with disease severity and complications. This case series presents five patients admitted to the King Abdullah Specialized Children Hospital (KASCH), an academic governmental tertiary center in Riyadh, Saudi Arabia. Table 1 shows the patients’ demographics and characteristics, and the treatment provided.

2 CASE SERIES

2.1 Case 1

A 10-month-old baby boy born preterm at 29 weeks, with a history of admission in the neonatal intensive care unit for respiratory distress syndrome, neonatal jaundice, and sepsis, was admitted to the pediatric intensive care unit (PICU) for bronchiolitis at 2 months of age. The baby was brought to the emergency room (ER) with a 1-week history of cough and shortness of breath. Laboratory investigations revealed leukocytosis, and chest radiograph (CXR) showed diffuse inhomogeneous patchy opacity. The patient was
not vaccinated for pertussis. Initially, azithromycin was administered for a differential diagnosis of pertussis, confirmed by respiratory-panel polymerase chain reaction (PCR). Echocardiography did not indicate pulmonary hypertension.

During PICU admission, the white blood cell (WBC) count was $77 \times 10^9/L$ (72% lymphocytes and 16% neutrophils), and a peak count of $99 \times 10^9/L$ (65% lymphocytes and 24% neutrophils) was recorded without organ failure. On day 2, the PICU team discussed the hyperleukocytosis and decided to intubate electively for leukoreduction, after which the WBC count decreased to $38 \times 10^9/L$. Following gradual pneumonia recovery after 7 days, the patient was extubated after appropriate weaning and discharged 2 weeks later (WBC count $15 \times 10^9/L$ during discharge).

### 2.2 | Case 2

A 7-month-old unvaccinated boy, born after an uneventful full-term pregnancy and perinatal course, was brought to the ER with cough and shortness of breath that had evolved over 6 days. There was positive history of sick contact. The patient was in mild respiratory distress and was clinically diagnosed with bronchiolitis. The initial WBC count was $17 \times 10^9/L$, and the patient was hospitalized. After 5 days, he showed worsening respiratory distress and persistent tachycardia up to 180 beats/min. A partial septic screen revealed progressive leukocytosis with dominant lymphocytosis (WBC $73 \times 10^9/L$; lymphocytes 41%, neutrophils 28%). The patient was transferred to the PICU and was given noninvasive ventilator support, but he had to be intubated after 2 days and required high ventilator settings and inotropic support with epinephrine. The WBC count progressively increased and peaked at $140 \times 10^9/L$, and antibiotic therapy comprising of azithromycin, piperacillin/tazobactam, and vancomycin was administered. *B. pertussis*, adenovirus, and bocavirus were confirmed by cultures and respiratory panel PCR. Laboratory tests showed persistent hyperleukocytosis, elevated liver enzymes, and coagulopathy, while echocardiography showed pulmonary hypertension.

The patient was switched to high-frequency oscillatory ventilation (HFOV) and inhalational nitric oxide (20 ppm). After the first session of leukoreduction, the WBC count decreased from $140 \times 10^9/L$ to $60 \times 10^9/L$, and transient clinical improvements in hypoxemia and hemodynamics were seen. However, he relapsed after 8 hours with rebound leukocytosis ($100 \times 10^9/L$). The second leukapheresis session decreased the WBC count to $47 \times 10^9/L$; however, within a few hours, the patient experienced a pulmonary hypertensive crisis that progressed to cardiac arrest with no return of spontaneous circulation (ROSC).

### 2.3 | Case 3

A 45-day-old baby girl was delivered after a full-term uneventful pregnancy via emergency cesarean section due to failure to progress, with no significant perinatal events. She was brought to an academic medical center with limited facilities with complaints of cough and shortness of breath. The patient was admitted to PICU for apnea due to acute bronchiolitis. Her clinical condition remained unaltered with mild respiratory distress and hypoxia that required O2 supplementation. Laboratory investigations showed progressive leukocytosis, where the WBC count increased from $27 \times 10^9/L$ during admission to $82 \times 10^9/L$ with 60% lymphocytes after 24 hours. Based on a suspected diagnosis of pertussis pending laboratory confirmation, azithromycin was started. Echocardiography showed moderate tricuspid valve regurgitation with an estimated gradient of 50 mm Hg. The patient was transferred to our hospital with diagnosis of pertussis and hyperleukocytosis for further management and leukapheresis.

On transfer to the PICU, the patient was hypoxic and hemodynamically unstable. Epinephrine, norepinephrine, and milrinone were administered, along with HFOV. However, her condition progressively worsened to multi-organ failure with acute kidney injury, encephalopathy, and coagulopathy. *B. pertussis* and rhinovirus were confirmed with respiratory-panel PCR. Broad-spectrum antibiotics (vancomycin and ceftriaxone) were administered along with azithromycin considering an iatrogenic infection. The patient underwent leukapheresis, and the WBC count dropped from $123 \times 10^9/L$ to $37 \times 10^9/L$. After 10 hours, there was rebound hyperleukocytosis (WBC count $100 \times 10^9/L$), and another leukapheresis session was scheduled. However, cardiac arrest occurred after initiation of the second session, and cardiopulmonary resuscitation was undertaken without ROSC.

### 2.4 | Case 4

A 40-day-old baby girl, born after a full-term uneventful pregnancy, was brought to the ER with cough, cyanosis, and signs of mild respiratory distress. Vital signs at presentation included heart rate (HR) of 130 beats/min and 93% oxygen saturation. The patient developed frequent paroxysmal cough followed by apnea in the ER, and she was admitted to the PICU. The initial WBC count was $32 \times 10^9/L$, and CXR showed bilateral patchy infiltration. Ampicillin and cefotaxime antibiotics were administered, but she had to be intubated because of repeated episodes of apnea and bradycardia. *B. pertussis* was confirmed on respiratory-panel PCR, and azithromycin was added to the antibiotic regimen. Echocardiography revealed tricuspid regurgitation with supra-systemic pulmonary hypertension. The patient was
placed on ionotrophic support with epinephrine and milrinone, as well as HFOV with nitric oxide (20 ppm). However, her condition progressively worsened to multi-organ failure with acute kidney injury, acute encephalopathy, acute liver injury, and disseminated intravascular coagulation. The WBC counts reduced from $69 \times 10^9/L$ (lymphocytes 63%, neutrophils 24%) to $19 \times 10^9/L$ after leukoreduction. Her respiratory status gradually worsened with signs of pulmonary hypertension. Hyperleukocytosis levels rebounded, and another leukapheresis session was performed, but pulmonary hypertensive crisis occurred that led to cardiac arrest without ROSC.

### 2.5 | Case 5

A 19-month-old unvaccinated healthy girl, delivered via normal spontaneous vaginal delivery after a full-term uneventful pregnancy, was brought to the ER by her parents for paroxysmal cough followed by cyanosis. The patient had been exposed to sick family members. She was hemodynamically stable (HR 130 beats/min), with signs of mild respiratory distress that necessitated administration of 1 L of O$_2$ via nasal cannula. Laboratory investigations revealed a WBC count of $115 \times 10^9/L$ (45% lymphocytes and 35% neutrophils), and the patient was admitted to the PICU, where her

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TABLE 1  Summary of patients’ characteristics and provided therapy

|              | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|--------------|--------|--------|--------|--------|--------|
| Age          | 10 mo  | 7 mo   | 45 d   | 40 d   | 19 mo  |
| Duration of symptoms | 7 d    | 6 d    | unknown| 2 d    | 4 d    |
| Immunization status       | Unvaccinated | Unvaccinated | Ineligible for vaccine | Ineligible for vaccine | Unvaccinated |
| Initial WBC          | 77     | 74     | 123    | 32     | 110    |
| Peak WBC            | 99     | 140    | 123    | 69     | 121    |
| Intervention for Leukoreduction | Leukapheresis | Leukapheresis | Leukapheresis | Leukapheresis | Hydroxyurea |
| Inotropic support    | None   | Epinephrine and Dopamine | Epinephrine and norepinephrine | Epinephrine, Norepinephrine, Milrinone, and vasopressin | None |
| Nitric oxide         | No     | Yes    | Yes    | Yes    | No     |
| Echocardiography timeline (to PICU admission) | Day 2 of admission | First 24 h | First 24 h | Day 3 of admission | Day 3 of admission |
| Echocardiography finding | Tricuspid insufficiency, pressure gradient = 28 mm Hg, no echo signs of pulmonary hypertension | Dilated right atrium and right ventricle, Mild tricuspid valve insufficiency, RVSP 50 | Moderate tricuspid regurgitation with estimated Pressure gradient 50 mm Hg, (RVSP 58, SBP 70) | Tricuspid regurgitation with gradient of 60 mm Hg and RVSP of 70 (SBP was 65 mm Hg, suprasystemic pulmonary hypertension) with dilated right ventricle and D-shaped left ventricle | Mild tricuspid valve insufficiency |
| Multi-organ failure   | No     | Yes (CNS, liver, kidney, DIC) | Yes (CNS, liver, kidney, DIC) | Yes (liver, kidney, DIC) | No |
| Coinfection          | None   | Adenovirus and Bocavirus | Human Rhinovirus | None | Adenovirus, Human Rhinovirus, and Parainfluenza 3 |
| PICU LOS            | 8 d    | 5 d    | 1 d    | 5 d    | 2 wk   |
| Hospital LOS        | 23 d   | 10 d   | 1 d    | 5 d    | 47 d   |
| Outcome             | Recovery | Mortality | Mortality | Mortality | Recovery |

Abbreviations: CNS, Central nervous system; DIC, Disseminated intravascular coagulation; LOS, Length of stay; PICU, Pediatric intensive care unit; RVSP, Right ventricle systolic pressure; SBP, Systolic blood pressure; WBC, white blood cell.
WBC count ranged between $110 \times 10^9/L$ and $122 \times 10^9/L$. Respiratory-panel PCR confirmed \textit{B pertussis}, adeno virus, human rhinovirus, and parainfluenza-3 virus coinfection. Echocardiography did not reveal any signs of pulmonary hypertension.

The PICU, infectious disease, and hematology teams decided not to undertake leukapheresis in view of the patient’s age and clinical stability. After 3 days of stable WBC count ($109-120 \times 10^9/L$), hydroxyurea 20 mg/kg was administered, which was later increased to 30 mg/kg and administered as a single daily dose. The patient remained hemodynamically stable, and her leukocytosis decreased gradually. The patient was shifted to the ward, weaned off O2, and discharged after a 12-day course of hydroxyurea (WBC count during discharge $36 \times 10^9/L$).

3 | DISCUSSION

Despite being a vaccine-preventable disease with routinely available effective antibiotics, pertussis remains a major global concern and carries a significant risk of morbidity and mortality.\textsuperscript{2,5} Hence, this mandates further research and resolution. Given the rarity of malignant pertussis and varied therapeutic options, a therapeutic trial might not be feasible. Therefore, reporting the clinical experiences of this disease is vital to shed light on the therapeutic management.

The surge in the global incidence of pertussis reflects disease awareness, advancement in diagnostic procedures, and possible changes in the \textit{B pertussis} strain.\textsuperscript{6} Pertussis usually has three phases: catarrhal phase (1-2 weeks), paroxysmal phase (2-6 weeks), and convalescence.\textsuperscript{2,7} Antibiotics and supportive respiratory care are the mainstay of pertussis management, regardless of the presenting syndrome.\textsuperscript{2,7} Antibiotic treatment is undertaken to attenuate disease severity and shorten the duration of illness, which decreases its contiguity.\textsuperscript{2,7} However, PICU admission might be needed, and this stage is considered critical in pertussis patients.\textsuperscript{8} Nonetheless, there is no defined standard clinical management for severe presentations of pertussis that are grouped under “malignant pertussis,” which is associated with higher mortality rates. Malignant pertussis is associated with respiratory failure, pulmonary hypertension, hyperleukocytosis, cardiogenic shock, and death.\textsuperscript{1,4}

The pathophysiological mechanism that mediates malignant pertussis is incompletely understood. A major part is attributed to the pertussis toxin (PT).\textsuperscript{9} The toxin-mediated effect on the respiratory epithelium generates increased secretions and plugging, leading to increased pulmonary vascular resistance (PVR).\textsuperscript{9,10} The PT triggers the frequently reported hyperleukocytosis causing sequestration, with or without thrombus formation, and induces rapidly progressing organ failure.\textsuperscript{9,11} Moreover, PT acts in line with other virulent factors, and induces the release of nitric oxide and promotes cytopathologic effects,\textsuperscript{12} which is supported by the finding that inhaled nitric oxide acts as a mortality predictor in patients with pertussis.\textsuperscript{12,13} Although physiologically sound, no alternative standard therapy for pertussis pulmonary hypertension exists. Accordingly, nitric oxide was used in majority of the reported cases in the literature as well as in three of our patients in this case series.\textsuperscript{11} All the aforementioned mechanisms have a common endpoint: a vicious cycle of ventilation-perfusion mismatching and pulmonary hypertension that leads to intractable cardiopulmonary failure and death.\textsuperscript{10,11,14,15}

The invasive nature of the therapeutic options for malignant pertussis and lack of standardized management strategies makes it important to recognize the predictive outcome indicators early in the course of illness for appropriate management. Imminent risk factors include high or rapidly increasing WBC count (>50-100 $\times 10^9/L$), persistent and consistent tachycardia, and high neutrophil/lymphocyte ratios.\textsuperscript{14} Other identified risk factors with variable correlation to morbidity and mortality include young infants (<2 months), seizure onset during illness, echocardiography findings of pulmonary hypertension, prematurity, and low birth weight.\textsuperscript{4,15,16}

Hyperleukocytosis is considered a precursor to respiratory failure and pulmonary hypertension in pertussis; hence, leukoreduction may be a therapeutic modality to prevent disease progression and mortality.\textsuperscript{9,11,17} Literature regarding leukoreduction in malignant pertussis is limited, and it shows conflicting results. Rowlands et al recommended leukoreduction for pertussis hyperleukocytosis in their cohort of five patients who underwent leukoreduction and had pulmonary hypertension, of which four survived.\textsuperscript{18} Berger et al’s cohort did not show any clear therapeutic advantages with the various treatments conducted, including leukoreduction. Their cohort included 14 patients, of which eight developed pulmonary hypertension and five died, implying that further studies are necessary to examine the implications of leukoreduction.\textsuperscript{8}

Leukoreduction is usually initiated based on a cut-off WBC count (>50-100 $\times 10^9/L$) and other risk factors.\textsuperscript{18,19} In our cases, leukoreduction was successful in the hyperleukocytosis case, where leukapheresis was performed prior to the onset of pulmonary hypertension. On the other hand, leukapheresis was initiated after the development of pulmonary hypertension in the other cases, and none of the patients survived despite a reduction in the WBC count. Thus, leukoreduction initiation for hyperleukocytosis prior to the onset of pulmonary hypertension is worth exploring.

Leukoreduction or extracorporeal membrane oxygenation (ECMO) alone is insufficient to manage pulmonary hypertension, and a combination of both may be warranted.\textsuperscript{20} Moreover, ECMO might be considered in high-risk patients.
with malignant pertussis who have already developed pulmonary hypertension. The cohort in the study by Rowlands et al reported survival of four out of five patients, and three of them underwent ECMO and leukoreduction sessions. The molecular mechanism of hydroxyurea action in malignant pertussis is based on theories of increased oxidative stress, which produces nitric oxide and alters blood cell adhesion to the endothelium. Maitre et al reported using hydroxyurea for malignant pertussis, showing clinical and biochemical responses. We simulated this approach in a toddler (Case 5) who was clinically stable to tolerate gradual WBC reduction and had asymptomatic pertussis-induced hyperleukocytosis, in order to avoid invasive leukoreduction. The patient did not show respiratory failure or pulmonary hypertension. In our clinical experience, we observed a satisfactory albeit slow biochemical response. The WBC reduction occurred gradually over a 10-14-day period, which was reasonable given the clinical status of the patient.

Identifying poor prognostic factors (age, tachycardia, seizures, WBC count 50-100 × 10^9/L, and neutrophil/lymphocyte ratio > 1) early in pertussis helps build an index of suspicion for potential complications. More importantly, patients can be stratified into high- and low-risk categories. In our series, age <2 months, elevated WBC count, and high

| Case 1 | Time 0 | 6 h | 12 h | 24 h | 36 h | 48 h | 72 h | 96 h | 120 h | 144 h |
|--------|--------|-----|------|------|------|------|------|------|-------|-------|
| WBC    | 77     | 55  | 99   | 38   | 21   | 21   | 15   | 25   | 18    |
| Neutrophil% | 14     | 14  | 24   | 47   | 38   | 53   | 46   | 31   |
| Lymphocyte% | 72     | 78  | 65   | 42   | 40   | 27   | 32   | 42   |
| N:L ratio | 0.19   | 0.17| 0.36 | 1.1  | 0.95 | 1.9  | 1.4  | 0.74 |
| HR     | 140-170| 135-165| 118-170| 150-190| 150-175| 120-170| 120-150| 140-180| 110-145| 120-140|

| Case 2 | Time 0 | 6 h | 12 h | 24 h | 36 h | 48 h | 72 h | 96 h | 120 h | 144 h |
|--------|--------|-----|------|------|------|------|------|------|-------|-------|
| WBC    | 74     | 87  | 120  | 119  | 132  | 140  | 100  | 69   |
| Neutrophil% | 28     | 38  | 51   | 51   | 66   | 64   | 63   | 41   |
| Lymphocyte% | 40     | 41  | 22   | 16   | 25   | 19   | 9    | 8    |
| N:L ratio | 0.7    | 0.9 | 2.3  | 3.1  | 2.6  | 3.3  | 7    | 5.1  |
| HR     | 110-150| 120-150| 120-160| 150-190| 150-190| 160-190| 160-190| 170-200| 170-190| 0     |

| Case 3 | Time 0 | 6 h | 12 h | 24 h | 36 h | 48 h | 72 h | 96 h | 120 h | 144 h |
|--------|--------|-----|------|------|------|------|------|------|-------|-------|
| WBC    | 123    | 43  | 37   | 59   | 49   |
| Neutrophil% | 46     | 67  | 75   | 68   | 67   |
| Lymphocyte% | 28     | 14  | 14   | 20   | 15   |
| N:L ratio | 1.6    | 4.7 | 5.3  | 3.4  | 4.4  |
| HR     | 170-220| 190-220| 200-220| 200-220| 200-220| 0     |

| Case 4 | Time 0 | 6 h | 12 h | 24 h | 36 h | 48 h | 72 h | 96 h | 120 h | 144 h |
|--------|--------|-----|------|------|------|------|------|------|-------|-------|
| WBC    | 32     | 19  | 55   | 69   | 22   | 43   | 10   | 19   |
| Neutrophil% | 22     | 20  | 31   | 24   | 49   | 45   | 30   | 55   |
| Lymphocyte% | 69     | 70  | 62   | 63   | 27   | 17   | 35   | 15   |
| N:L ratio | 0.32   | 0.28| 0.5  | 0.38 | 1.8  | 2.6  | 0.8  | 3.6  |
| HR     | 120-160| 120-150| 42-165| 60-165| 130-170| 170-185| 165-195| 55-195| 200-220| 0     |

| Case 5 | Time 0 | 6 h | 12 h | 24 h | 36 h | 48 h | 72 h | 96 h | 120 h | 144 h |
|--------|--------|-----|------|------|------|------|------|------|-------|-------|
| WBC    | 110    | 115 | 107  | 122  | 120  | 113  | 118  | 109  | 94    |
| Neutrophil% | 35     | 29  | 29   | 30   | 32   | 32   | 18   | 17   | 18    |
| Lymphocyte% | 45     | 61  | 54   | 61   | 53   | 62   | 73   | 75   | 73    |
| N:L ratio | 0.78   | 0.4 | 0.54 | 0.49 | 0.6  | 0.52 | 0.24 | 0.23 | 0.25  |
| HR     | 145-170| 125-165| 115-170| 130-150| 110-150| 120-160| 110-150| 110-150| 110-155| 0     |

Abbreviations: HR, Heart rate; N:L ratio, Neutrophil/lymphocyte ratio; WBC, White blood cell.

TABLE 2 Patients’ trends of WBC count, neutrophil-lymphocyte ratio, and heart rate throughout their PICU stay
neutrophil/lymphocyte ratio uniformly carried a higher probability of developing pulmonary hypertension, and eventually, death. We observed that a high neutrophil/lymphocyte ratio was associated with worsening of the disease course and mortality (Cases 2-4, Table 2). This corroborates with a retrospective cohort study by Ganeshalingham A et al, wherein all children with malignant pertussis had neutrophil/lymphocyte ratios >1.16 Having any of these risk factors puts the patient in the high-risk category, even before the appearance of any signs of organ dysfunction. This was evident in three of our patients, who progressed after a variable time gap of having the risk factors to multi-organ failure, specifically acute kidney injury, acute encephalopathy, and disseminated intravascular coagulation with or without acute liver injury. Linking organ dysfunction directly to hyperleukocytosis needs autopsy confirmation, which was not performed in our cases,11,21,22

Evidence of risk factors should trigger close clinical and laboratory monitoring and early screening for pulmonary hypertension, immediately after recognizing the patient as high risk, using echocardiography to support an anticipatory management approach. Leukoreduction is an option in high-risk patients. Careful observation with supportive respiratory care is reasonable for low-risk patients. Hydroxyurea, an option for pertussis associated-hyperleukocytosis, can be used for older infants and toddlers and as a “stop-gap” during transfer and further intervention at another center.

In this case series, none of the patients who developed pulmonary hypertension survived, despite undergoing leukapheresis. ECMO was not offered to any patients. Hence, no recommendations based on this series can be made for the treatment modalities in pediatric malignant pertussis. Further reports exploring the hypothesized benefit of early initiation of leukoreduction prior to pulmonary hypertension initiation, and combination of ECMO and leukoreduction are needed.

In conclusion, close monitoring of HR, WBC count, and neutrophil/lymphocyte ratio is important for early recognition of children at a risk of malignant pertussis, and enable early PICU transfer for management with leukoreduction and ECMO. Due to the lack of evidence regarding the efficacy of leukoreduction or hydroxyurea, multidisciplinary discussion and local guidelines regarding treatment are recommended.

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CONFLICT OF INTEREST
The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS
Nedaa Aldairi: collected and analyzed the data, did the literature review, drafted the manuscript as submitted and agrees to be accountable for all aspects of the work. Hamza Alali: participated in collecting the data and critically reviewed the manuscript for important intellectual content. Yasser Kazzaz: participated in collecting the data and critically reviewed and supervised the writing of the manuscript.

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REFERENCES
1. Tian SF, Wang HM, Deng JK. Fatal malignant pertussis with hyperleukocytosis in a Chinese infant: a case report and literature review. Medicine (Baltimore). 2018;97(17):e0549.
2. Gabutti G, Azzari C, Bonanni P, et al. Pertussis. Hum Vaccin Immunother. 2015;11(1):108-117.
3. Donoso A, Arriagada D, Cruces P, Diaz F. Severe pertussis: state of the art. Rev Chilena Infectol. 2012;29(3):290-306.
4. Carbonetti NH. Pertussis leukocytosis: mechanisms, clinical relevance and treatment. Pathog Dis. 2016;74(7):ftw087.
5. Sealey KL, Belcher T, Preston A. Bordetella pertussis epidemiology and evolution in the light of pertussis resurgence. Infect Genet Evol. 2016;40:136-143.
6. Syed MA, Pertussis BNF. A reemerging and underreported infectious disease. Saudi Med J. 2014;35(10):1181-1187.
7. Snyder J, Fisher D. Pertussis in childhood. Pediatr Rev. 2012;33(9):412-420; quiz 420-411.
8. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatr Crit Care Med. 2013;14(4):356-365.
9. Nieves D, Bradley JS, Gargas J, et al. Exchange blood transfusion in the management of severe pertussis in young infants. Pediatr Infect Dis J. 2013;32(6):698-699.
10. Maitre G, Schaffner D, Natterer J, et al. Leukemoid reaction in infant pertussis: is there a place for hydroxyurea? A case report. Front Pediatr. 2018;6:261.
11. Palvo F, Fabro AT, Cervi MC, Aragon DC, Ramalho FS, Carlotti A. Severe pertussis infection: a clinicopathological study. Medicine (Baltimore). 2017;96(48):e8823.
12. Winter K, Zipprich J, Harriman K, et al. Risk factors associated with infant deaths from pertussis: a case-control study. Clin Infect Dis. 2015;61(7):1099-1106.
13. Flak TA, Goldman WE. Autotoxicity of nitric oxide in airway disease. Am J Respir Crit Care Med. 1996;154(4 Pt 2):S202-S206.
14. Ganeshalingham A, McSharry B, Anderson B, Grant C, Beca J. Identifying children at risk of malignant Bordetella pertussis infection. Pediatr Crit Care Med. 2017;18(1):e42-e47.
15. Onoro G, Salido AG, Martinez IM, Cabeza B, Gillen M, de Azagra AM. Leukoreduction in patients with severe pertussis with hyperleukocytosis. Pediatr Infect Dis J. 2012;31(8):873-876.
16. Murray EL, Nieves D, Bradley JS, et al. Characteristics of severe Bordetella pertussis infection among infants ≤90 days
of age admitted to Pediatric Intensive Care Units - Southern California, September 2009-June 2011. J Pediatric Infect Dis Soc. 2013;2(1):1-6.

17. Sawal M, Cohen M, Irazusta JE, et al. Fulminant pertussis: a multi-center study with new insights into the clinico-pathological mechanisms. Pediatr Pulmonol. 2009;44(10):970-980.

18. Rowlands HE, Goldman AP, Harrington K, et al. Impact of rapid leukodepletion on the outcome of severe clinical pertussis in young infants. Pediatrics. 2010;126(4):e816-e827.

19. Pilorget H, Montbrun A, Attali T, et al. Malignant pertussis in the young infant. Arch Pediatr. 2003;10(9):787-790.

20. Halasa NB, Barr FE, Johnson JE, Edwards KM. Fatal pulmonary hypertension associated with pertussis in infants: does extracorporeal membrane oxygenation have a role? Pediatrics. 2003;112(6 Pt 1):1274-1278.

21. Scanlon K, Skerry C, Carbonetti N. Association of pertussis toxin with severe pertussis disease. Toxins (Basel). 2019;11(7):373.

22. Straney L, Schibler A, Ganeshalingham A, et al. Burden and outcomes of severe pertussis infection in critically ill infants. Pediatr Crit Care Med. 2016;17(8):735-742.

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