Pertussis requiring intensive care

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Supplemental tables 1 and 2 are available at <http://adc.bmj.com/supplemental>

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Objectives: To describe children with pertussis who require intensive care.

Design, setting and patients: An audit in Auckland, New Zealand, of pertussis admissions to the national paediatric intensive care unit (PICU) from 1991 to 2003.

Results: 72 children, 97% of whom were <12 months old. The annual number of cases increased with time ($p=0.04$). Forty patients (56%) were coughing for less than 8 days before admission. Apnoea or paroxysmal cough was present in 33 (83%) of these children. Thirty five (49%) received assisted ventilation. Four died. 19% were readmitted to PICU. Those readmitted presented with more atypical disease and had a shorter first admission but longer total PICU admission (9 vs 5 days, $p=0.009$). Of the 58 children from Auckland, nine either died (three) or had subsequent respiratory or neurodevelopmental problems (six). There was an increased risk (relative risk, 95% CI) of death or disability associated with having a co-morbidity (RR=5.56, 1.50 to 8.15), an elevated lymphocyte count (RR=5.75, 1.54 to 13.65), presenting with seizures/encephalopathy (4.87, 1.18 to 8.34) or shock (6.50, 1.89 to 8.94), having a PIM score of 1% or more (RR=6.20, 1.22 to 21.72), any abnormal neurological signs (RR=9.65, 3.32 to 15.23) or being readmitted to PICU (RR=4.63, 1.44 to 8.82).

Conclusions: Apnoea and paroxysmal cough are key symptoms of pertussis in those with shorter cough duration. Death or disability are frequent. Clinical factors define children at increased risk of these poor outcomes. Early discharge from PICU is associated with an increased risk of readmission and poor outcome.

Severe pertussis in young infants remains difficult to treat. The limited success of extra-corporeal membrane oxygenation (ECMO) and oscillatory ventilation has been reported.^{1 2}

Although the risk factors for fatal disease have been defined, the clinical course of the disease in children requiring intensive care for pertussis is incompletely described.^{2–4} The largest reported series included 24 children in Sydney between 1978 and 1989, and 25 in London paediatric intensive care units (PICUs) between 1998 and 2000.^{5 6}

New Zealand (NZ) has high pertussis hospitalisation rates. The average annual rates in the 1990s and 2000s for infants were 222 and 293 per 100 000 person-years, respectively.⁷ In comparison, the rate (per 100 000) in the United States was 33 in 1990–2000 and 69 in England and Wales in 1995.^{8–10}

The Starship Children's Hospital PICU is the country's sole PICU. It serves 850 000 children aged 0–14 years in NZ¹¹ and so has more experience with pertussis than most.

This study aimed to describe our pertussis intensive care experience and to identify factors associated with death or subsequent disability.

METHODS

The audit included all PICU pertussis admissions from December 1991, when the unit opened, to December 2003. Hospital administrative approval and confirmation that ethical approval was not required were obtained.

Pertussis cases were identified from three sources. Firstly, a search of the PICU database, using the principal PICU discharge diagnosis of pertussis, identified patients. Second, using the same database, all discharge diagnoses of apnoea or pneumonia where pertussis had been queried were retrieved. These were included if there was:

- A positive culture or polymerase chain reaction (PCR) result for *Bordetella pertussis*. The PCR assay used primers selected from insertion sequence 481.^{12–16}
- An illness consistent with pertussis for which no alternative cause was identified. This included apnoea and a paroxysmal cough with cyanosis or desaturation. Those with wheeze as a predominant symptom were excluded.

Third, the hospital laboratory provided a list of all *B pertussis* isolates (from 1996) and all positive *B pertussis* PCR assays (from 1998). These were cross-checked with the PICU database.

Data were abstracted from the PICU database and the hospital records. Variables included those describing demographics, the presenting illness, pre-hospital care, immunisations and household exposures, clinical status on presentation to the PICU, disease severity, treatment and complications.

The NZ immunisation schedule includes three infant pertussis vaccine doses, given at ages 6 weeks and 3 and 5 months. A 15-month dose was added in 1996, acellular vaccine was introduced in 2000 and a 4-year booster dose was included in 2002.¹⁷ Immunisation coverage surveys from the 1990s indicate that the three-dose infant series was received by between 80% and 90% of children with 50%–60% receiving these immunisations on time.^{18 19}

Weight for age z scores were calculated in Epi Info 2000 (CDC, Atlanta, GA) using the WHO/CDC reference data.²⁰ Peripheral leukocyte and lymphocyte counts were considered elevated if above the 95% confidence limits for age.²¹

An electronic database was created from the case record forms (Microsoft Access, Seattle, WA). Data analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC).

Abbreviations: ECMO, extra-corporeal membrane oxygenation; NZ, New Zealand; PICU, paediatric intensive care unit

Time trends were examined using Poisson regression. Logistic regression was used to identify variables associated with death or disability. As the odds ratios were determined on a cohort in which death or disability was a relatively frequent outcome, the relative risk estimated from the odds ratio was adjusted to more accurately represent the true relative risk.²²

RESULTS

There were 72 children. Pertussis was the PICU discharge diagnosis in 66. Another 38 in whom pertussis was queried were identified and five of these were included, four of whom were PCR positive. The PCR negative infant had paroxysms, whoop, seizures and a respiratory arrest. One other patient was identified from laboratory records (PCR positive).

The 33 of 38 children with PICU discharge diagnoses of apnoea or pneumonia in whom pertussis was queried were excluded as follows: PCR negative (11), culture negative but PCR not performed (three), wheeze (five), RSV identified but no laboratory investigations for pertussis (six), alternative cause for symptoms (two) and insufficient symptoms to diagnose pertussis (six).

Demographics and immunisation

The demographics of the children with pertussis are shown in table 1.

Fifty nine children (81%) were less than 3 months old. Only two were more than 1 year old: one aged 4 with reduced consciousness and multiple seizures and one aged 7 (described previously), who required ventilatory support for hypoventilation.²³

Twenty eight children (39%) were less than 6 weeks old. Of the remaining 44, only 13 (30%) were fully immunised for age. Twenty three (52%) of these 44 had received no immunisations. Immunisation data by age group are shown in supplemental table 1 which is available at <http://adc.bmj.com/supplemental>.

Table 1 Demographics of the 72 children with pertussis admitted to the PICU

Variable	
Female, n (%)	38 (53)
Weight z score, mean, SD*	-0.14 (1.15)
Prematurity, n (%)	19 (26)
Co-morbidities (n = 10), n (%)†	
Congenital heart disease	3 (4)
Chronic respiratory disease	3 (4)
Other co-morbidity‡	5 (7)
Social deprivation index quintile (n = 67), n (%)§	
1	5 (7)
2	7 (11)
3	5 (7)
4	18 (27)
5	32 (48)
Ethnicity, n (%)	
European	24 (33)
Maori	26 (36)
Pacific	21 (29)
Other	1 (2)
Other household members with cough, n (%)¶	40 (71)
Age group household members**	
Preschool only	11 (29)
School only	6 (15)
Adult(s) only	6 (15)
Adults and children	16 (41)

*Age z score adjusted for prematurity, n = 71; †one had congenital heart disease and chronic respiratory disease; ‡includes one with multicystic dysplastic kidney and failure to thrive, and four with recent hospital admissions for pneumonia (two), inguinal hernia repair (one) and incision/drainage of abscess (one); §social deprivation index 1 = household in least deprived quintile, 5 = household in most deprived quintile; ¶n = 56; **n = 39.

Ten children (14%) had a co-morbidity, most frequently congenital heart or chronic respiratory disease. Four of these 10 had been recently hospitalised. There was at least one other household member with cough for 40 (71%) of 56 children where this information was recorded.

Temporal and regional admission patterns

Annual pertussis admissions are shown in fig 1.²⁴⁻²⁷ There was a significant increase in annual number of cases with time ($p = 0.04$) (as data were not collected for the entire year, 1991 was not included in this analysis).

There was a median (25, 75th centile) of 1 (0, 3) day between hospital and PICU admission. Twenty (29%) of 70 patients were admitted to the PICU on the day of hospital admission. Fourteen (19%) were transferred from other NZ regions. Neither the median days between hospital and PICU admission (1.0 vs 2.0, $p = 0.66$) nor the proportion admitted to the PICU on the day of presentation (30% vs 23%, $p = 0.74$) varied for Auckland versus other regions.

Presenting clinical characteristics

The presenting clinical characteristics are shown in table 2.

Cough was present for a median (25, 75th centile) of 7 (4, 14) days before admission. Two patients presented with no cough. Of the case-defining symptoms, paroxysmal cough (75%) and apnoea (47%) were the most frequent. On admission only 31% of children satisfied the pertussis notification case definition of cough lasting longer than 2 weeks and one or more of paroxysmal cough, cough ending in vomiting or apnoea, and inspiratory whoop for which there is no other known cause.²⁸ This small proportion was primarily because of short cough duration.

In 61% of patients, two or more case-defining symptoms were present before hospital admission. The only symptoms occurring in isolation were paroxysmal cough (11/19 with paroxysmal cough) and apnoea (8/19 with apnoea). One of those with apnoea had no cough.

Paroxysmal cough was present in fewer patients coughing for 1 week or less compared with those coughing for longer (65% vs 93%, $p = 0.005$). In contrast, the proportion with apnoea (48% vs 47%, $p = 0.95$) or whoop (20% vs 17%, $p = 0.72$) did not differ.

Leukocytosis was present in 42 (61%) and lymphocytosis in 28 (41%) of 69 children. Neither varied with age or non-immunisation (data not shown). Chest radiographs were abnormal in 52 (72%). Lobar consolidation was present in 35/52 (67%). Four had a pleural effusion. Consolidation frequently involved multiple lobes.

Laboratory confirmation of *B pertussis* infection was achieved for 49 (68%). Confirmation was by culture and/or PCR in 48 and by paired serology in the 7-year-old child.²³ Laboratory

Figure 1 Annual number of children with pertussis admitted to the paediatric intensive care unit (PICU) and national pertussis hospital discharge rate.

Table 2 Clinical characteristics on hospital presentation

Symptom	n (%)
Cough duration pre-admission*	
0–7 days	40 (58)
8–14 days	15 (21)
15 days or longer	15 (21)
Presence of any case-defining symptom	63 (88)
Paroxysmal cough	54 (75)
Apnoea at home	34 (47)
Post-tussive vomit	20 (28)
Whoop	13 (18)
Number of case-defining symptoms	
0	9 (13)
1	19 (26)
2	32 (44)
3 or 4	12 (17)
Lymphocyte count ($\times 10^9/l$)†	
0–9	24 (35)
10–14	15 (22)
15–24	13 (19)
≥ 25	17 (25)
Laboratory confirmation of <i>Bordetella pertussis</i> infection	49 (68)
Culture	11 (22)
PCR	12 (25)
Culture and PCR	25 (51)
Serology‡	1 (2)
Laboratory investigation for viral pathogens	43 (60)
Respiratory syncytial virus	7 (44)
Picornavirus	3 (19)
Enterovirus	2 (13)
Adenovirus	1 (6)
Parainfluenza	1 (6)
Cytomegalovirus	1 (6)
Parainfluenza virus+RSV	1 (6)

*n=70; †n=69; ‡a 7-year-old child with pertussis encephalopathy previously described.¹⁴

confirmation was achieved for 12/22 (55%) from 1991–1995, for 7/15 (47%) from 1996–1999 and for 30/35 (86%) from 2000–2003 ($p = 0.007$). PCR positive cases accounted for most of this increase (14% in 1991–1995, 14% in 1996–1999, and 73% in 2000–2003; $p < 0.001$).

Cough duration, case-defining symptoms, satisfaction of clinical case definition or proportion with lymphocytosis did not vary in comparisons between those with or without laboratory confirmation (the data are shown in supplemental table 2 which is available at <http://adc.bmj.com/supplemental>).

Presenting illness and clinical course in the PICU

The presenting illness and clinical course in the PICU are shown in tables 3 and 4.

Table 3 Clinical presentation on admission to the PICU*

Variable	n (%)
Reason for PICU admission	
Apnoea	59 (82)
Bradycardia	45 (63)
Pneumonia	20 (28)
Repeated desaturation	17 (24)
Intubated pre-arrival	9 (13)
Respiratory arrest	8 (11)
Seizures or encephalopathy	7 (10)
Shock	6 (8)
Cardiopulmonary arrest	5 (7)
PIM score	
<1%	24 (33)
1–4%	29 (40)
$\geq 5\%$	19 (27)

*n=72.

PIM, paediatric index of mortality is percentage probability of death at the time of first contact with the PICU team.⁴¹

Apnoea (82%) and bradycardia (63%) were the most frequent reasons for PICU admission. For most patients (86%) more than one clinical indication was present.

Fourteen patients (19%) were readmitted to the PICU from the hospital ward. The median (25, 75th centile) time between discharge and readmission to the PICU was 3 (1, 10) days. While the length of the first PICU admission was shorter in those readmitted (3 vs 5 days, $p = 0.03$), the total number of PICU days was greater (9 vs 5 days, $p = 0.009$). The 14 were readmitted because of recurrent or increased severity of coughing and/or cyanotic episodes (five), recurrent apnoea (two), respiratory deterioration (three), shock and pulmonary hypertension (two), seizures (one) and haemolytic uraemic syndrome (one).

Age, prematurity, immunisations received, cough duration or reason for PICU admission did not differ for those readmitted versus those not readmitted. The median number of case-defining symptoms (1 vs 2, $p = 0.048$) and the proportion with paroxysmal cough (50% vs 81%, $p = 0.03$) was smaller in those readmitted.

Apnoea, bradycardia and cyanosis occurred in most patients while they were in the PICU. Neurological abnormalities were observed in 13 (18%). Ten had more than one abnormality. All six with seizures also had other neurological abnormalities.

Thirty five children (49%) received assisted ventilation for a median (25th, 75th centiles) of 4 (2, 9) days. Most (81%) treated with continuous positive airway pressure also received intermittent mandatory ventilation. Eleven (15%) received inotropes and six (8%) nitric oxide.

Outcomes: readmissions, disability and death

Outcomes (readmissions, disability and death) are shown in table 5.

Four children (6%) died, one each year from 2000 to 2003. All were less than 6 weeks old. Three had co-morbidities: one had poor weight gain, one intrauterine growth retardation and one failure to thrive and a multicystic dysplastic kidney. All had lobar consolidation, three had extensive multilobar pneumonia and two had pleural effusions. All died despite ventilation, nitric oxide and multiple inotropes. Three died within 3 days of PICU admission. In the remaining case, ECMO was withdrawn after 3 weeks following multiple failed attempts at weaning and a CT chest scan showing diffuse pulmonary infarction.

Outpatient follow-up data were available for the 58 patients from Auckland. Six (10%) who had subsequent neurodevelopmental problems, were all neurologically abnormal in the PICU. Four of these also had subsequent respiratory disease, one of whom had preceding respiratory disease. To identify factors associated with poor outcome, the nine from Auckland who died (three) or had subsequent respiratory or neurodevelopmental problems (six) were compared with the 49 who survived.

Six of the nine with a poor outcome were less than 2 months old and eight had received no immunisations. After adjustment for age and immunisation status, there was an increased risk of poor outcome associated with the presence of a co-morbidity ($RR = 5.56$), a lymphocytosis ($RR = 5.75$), PICU admission because of seizures or encephalopathy ($RR = 4.87$) or shock ($RR = 6.50$), having a PIM score of 1% or more ($RR = 6.20$), any abnormal neurological signs while in the PICU ($RR = 9.65$) or being readmitted to the PICU ($RR = 4.63$) (table 5).

DISCUSSION

The atypical presentation of severe pertussis was apparent. Of the case-defining symptoms, paroxysmal cough and apnoea were the most important diagnostically and in over half of the patients they were the only case-defining symptom. Apnoea

Table 4 Clinical features and treatment of pertussis while in the PICU

Variable	n (%) or median (25th, 75th centiles)
Number readmitted to the PICU	14 (19)
Number of PICU admissions	
1	58 (81)
2	8 (11)
3	3 (4)
4	3 (4)
Total days in PICU	5 (3, 10)
Clinical signs in PICU	
Apnoea	54 (75)
Bradycardia	56 (78)
Cyanosis	60 (83)
Abnormal movements	12 (17)
Abnormal long tract signs	9 (13)
Altered mental state*	7 (10)
Seizures	6 (8)
Antibiotic treatment prior to PICU admission (n = 53)†	
Erythromycin	21 (29)
Erythromycin plus other antibiotics	15 (21)
Other antibiotics	17 (24)
None	19 (26)
Erythromycin given in PICU	
Yes	69 (96)
No‡	3 (4)
Duration of erythromycin treatment, days (n = 61)	14 (10, 14)
Assisted ventilation (n = 35)	
CPAPs	16 (22)
Conventional ventilation	32 (44)
HFOV	3 (4)
ECMO	1 (1)
Ventilation days (n = 35)	4 (2, 9)

*Includes being less responsive than normal (eg, unable to fix and follow) or less able to function normally (eg, suck); †other antibiotics included amoxycillin, augmentin, ceclor, cefuroxime and cefotaxime; ‡none of these treated with erythromycin prior to PICU admission; §13 of these 16 also received conventional ventilation or HFOV or ECMO. ECMO, extra-corporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation.

was frequently a presenting symptom in those with cough for 1 week or less. It is of note that the current Australian and American pertussis case definitions do not include apnoea.^{29 30} This study indicates that apnoea should be one of the case-defining symptoms.

This retrospective study will have underestimated the true number of pertussis PICU admissions. Cases where pertussis was a differential diagnosis were excluded in some instances without adequate laboratory investigation. A recent prospective laboratory study from London identified pertussis in 20% of infants admitted to a PICU with respiratory failure, apnoea or bradycardia or an acute life threatening event.⁶

Death and disability occurred frequently. Many of the risk factors for these poor outcomes were already known.^{2 31} The increased risk of poor outcome associated with PICU readmission from the ward has not been described previously. PICU admission criteria were similar to those for any tertiary unit in the developed world and include recurrent apnoea or significant or insipient respiratory failure. Discharge from the PICU only occurred after a period of clinical stability. Thus, it seems unlikely that the need for readmission reflected local practice.

It is more likely that readmission occurred in those with more severe disease. That a smaller proportion of these patients had paroxysmal cough and that they initially presented with fewer case-defining symptoms implies earlier presentation. The reasons for readmission were consistent with disease evolution. For national or regional PICUs, infants with possible pertussis should remain on the ward at the tertiary centre for longer than would otherwise be the case before returning to the referring hospital.

The annual number of pertussis PICU admissions increased from 1992 to 2003. PCR helped confirm cases in more recent years. However, the clinical illness was not different in those with or without laboratory confirmation of *B pertussis* infection. Hence PCR did not identify a milder spectrum of illness. This increase is consistent with the increasing pertussis hospitalisation rate in NZ over the past four decades, which was apparent well before PCR became available.⁷ Recent increases in severe disease in young infants have also been reported from the United States.⁴

This study had only modest power. The scope was also limited by the retrospective data collection and the incomplete follow-up. This limited our ability to fully investigate ventilatory and circulatory support (eg, the contribution that mean airway pressure, and pulmonary and systemic arterial pressures make to outcome).^{4 32} Prospective enrolment into a multicentre study appears necessary.

How can we reduce severe pertussis in young infants? Immunisation reduces the risk of severe disease.¹⁰ Half of the

Table 5 Factors associated with death or subsequent respiratory or neurodevelopmental problems in children with pertussis admitted to the PICU

Clinical characteristics	Poor outcome*		Unadjusted relative risk (95% CI)	Adjusted relative risk† (95% CI)
	Yes (n ₁ = 9), n (%)	No (n ₂ = 49), n (%)		
Past medical history				
No immunisations	8 (89)	35 (71)	2.77 (0.54 to 11.77)	3.64 (0.58 to 12.61)
Co-morbidity present	3 (33)	4 (8)	3.62 (0.94 to 6.80)	5.56 (1.50 to 8.15)
Presenting symptoms and laboratory data				
Post-tussive vomiting pre-admission	5 (56)	11 (22)	3.24 (0.99 to 6.93)	3.04 (0.88 to 6.76)
Lymphocytosis	7 (78)	15 (33)	5.26 (1.48 to 12.85)	5.75 (1.54 to 13.65)
Reasons for PICU admission				
Pneumonia	4 (44)	8 (16)	3.06 (0.87 to 6.39)	3.35 (0.95 to 6.83)
Seizures or encephalopathy	3 (33)	2 (4)	5.38 (1.54 to 8.44)	4.87 (1.18 to 8.34)
Shock	3 (33)	1 (2)	6.80 (2.22 to 8.95)	6.50 (1.89 to 8.94)
Clinical course in the PICU				
PIM score of ≥1%	8 (89)	27 (55)	5.34 (1.08 to 20.99)	6.20 (1.22 to 21.72)
Any abnormal neurological signs‡	6 (67)	5 (10)	8.82 (3.10 to 14.56)	9.65 (3.32 to 15.23)
Readmitted to the PICU	5 (56)	8 (16)	4.31 (1.36 to 8.41)	4.63 (1.44 to 8.82)

*Death (n = 3) or subsequent respiratory or neurodevelopmental problems (n = 6); †adjusted for age (less than 2 months, 2 months and >2 months) and immunisation status (no immunisations, some immunisations); ‡includes abnormal movements, long tract signs, altered mental status or seizures.

What is already known about this topic

- Severe pertussis in infants remains difficult to treat and deaths occur despite admission to a paediatric intensive care unit (PICU).
- Although factors associated with an increased risk of fatal pertussis have been identified (young age, pneumonia, seizures, leukocytosis and hypoxemia), the clinical course of severe pertussis is not well described.

What this study adds

- In over half of those requiring intensive care, cough is present for 1 week or less prior to admission. Apnoea or paroxysmal cough are present in most (83%) children with such short cough duration.
- Especially in children with clinically atypical disease, care must be taken not to discharge the patient from the PICU too soon as early discharge from the PICU is associated with an increased risk of readmission and of poor outcome.

children in this series who were old enough had received no immunisations. Thus the immediate intervention is on time delivery of the current immunisation schedule.

Other potential strategies include reducing the infectivity of contacts, by vaccinating family members and health care workers, and earlier commencement of immunisation. Acellular pertussis vaccines may enable immunisation schedules to start at, and protect from, a younger age.³³

Household contacts appeared to be the key source of infection for these infants. This wide age range of contacts is likely due to a combination of the mediocre immunisation coverage in New Zealand and the endemic nature of pertussis in adults, adolescents and school-aged children.^{34–36}

The revision of the NZ immunisation schedule in 2006 to include a booster dose of pertussis vaccine at 11 years of age should reduce the infectivity of adolescents.³⁷ Subsequent boosters, either of the whole population or of expectant parents, should also be considered.

Infants die of pertussis despite ventilation, nitric oxide and inotropes. Only 30% of cases treated with ECMO survive.¹ Thus novel or disease specific treatments seem necessary. Recent reports indicate that haemofiltration, exchange transfusion and pulmonary vasodilators that do not act via the adrenergic system, namely milrinone and sildenafil, may be useful.^{38–40} Risk factors for poor outcome identified on admission should guide subsequent PICU care and identify children for whom such interventions are most appropriate.

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