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A 4 Year Prospective Study to Determine Risk Factors for Severe Community Acquired Pneumonia in Children in Southern China

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Summary. Background: Pneumonia is the major cause of death under 5 years. With high CAP numbers in China and growing access to PICUs, factors associated with severe CAP need to be determined to optimize care. Objective: To prospectively determine PICU CAP admission features and outcomes. Methods: A 4 year prospective study of CAP aged 1 month to <14 years admitted to PICU, Children's Hospital Affiliated to Soochow University, China. All were managed in a standard manner. Clinical, laboratory, and imaging findings were collected systematically. All received antibiotics. Results: Eight hundred ten (7%) of 10,836 CAP hospital admissions needed PICU. Seven hundred seven (87%) were enrolled. PICU CAP children were young (76% ≤ 12 months) and 33% had co-morbid conditions; 21% congenital heart disease.21% required mechanical ventilation. The average length of PICU stay was 5 days (range, 3–27). The case fatality rate was 5.8%. Viruses were detected in 38%, RSV 24%; bacteria in 23%, *Streptococcus pneumoniae* 7%, *Haemophilus influenza b* 4%, *Mycoplasma* 11%. On single factor analysis, PICU admission respiratory rate >70/min, grunting/groaning, head nodding, cyanosis, and anemia were associated with respiratory failure and with fatality. On multivariate analysis only presence of congenital heart disease, Trisomy 21 and immunodeficiency correlated with fatality; not microbe nor PICU findings. Conclusions: Young age and underlying congenital heart disease were associated factors for PICU support in CAP in China. Early referral if altered sensorium, high respiratory rate, head nodding, grunting and anemia, and universal access to conjugated vaccines may decrease morbidity and mortality. **Pediatr Pulmonol. 2013; 48:390–397.** © 2012 Wiley Periodicals, Inc.

Key words: Community acquired pneumonia; acute lower respiratory tract infection; children; hospitalized; developing country; intensive care; risk factors; China.

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INTRODUCTION

Pneumonia is well recognized as the leading cause of death for children under the age of 5 years worldwide with more children in this age group dying from pneumonia than from AIDS, malaria and tuberculosis combined.[1] In this age group, pneumonia is responsible for about 19% of all deaths.[1,2] Of all community acquired pneumonia (CAP) cases, an estimated 7–13% are severe enough to require hospitalization.[1] Of the estimated 156 million new episodes of childhood pneumonia each year worldwide, 151 million episodes are in the developing countries.[1] Simply because of their very large populations, the majority of cases occur in India (43 million), China (21 million), and Pakistan (10 million), with additional high numbers in Bangladesh, Indonesia, and Nigeria (6 million each). All are developing countries with emerging economies; some more than others. In 2010–2011, their gross domestic product based on purchasing-power-parity (PPP) per capita range from China 92nd of 183 countries at $8,382, Indonesia

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122nd at $4666, India 129th at $3,694, Nigeria 141st $2,578, and Bangladesh 155th at $1,693.[3] Of note, Norway was in 4th place with $53, 471 per capita.

Given the very high number of children in China and India with CAP and the growing access to intensive care in these countries, factors associated with very severe CAP pneumonia requiring pediatric intensive care (PICU) need to be determined to better optimize care programs and outcomes. A Medline search in 2006 using the terms ''pneumonia or acute lower respiratory infection, children, risk factors, developing country, hospitalized'' revealed only 26 studies none of which focused on risk factors for need for intensive care nor subsequent outcomes. Substituting the term China or India for developing country in the search added no studies. A broader search with the terms ''community acquired pneumonia, children, intensive care'' revealed few relevant articles in a developing country among the 35 retrieved. None of those retrieved were particularly helpful as the PICU cohort was too small to delineate risk factors for ventilation and fatality,[4] the study were focused on hospital not PICU factors,[5] or was predominately centered on a specific pathogen.[6,7] Hence in 2007, a 4 year prospective study in a large children's hospital in southern China was under taken to determine presenting PICU admission features, factors associated with need for mechanical ventilation, length of stay and risk of fatality in children with community acquired pneumonia severe enough to require intensive care.

METHODS

Patients and Clinical Samples

This 4 year prospective study was carried out from January 1, 2007 to December 31, 2010 in the 10 bed PICU, Children's Hospital Affiliated to Soochow University. This Children's Hospital serves as the pediatric tertiary care referral center for admissions for those <14 years of age in the Greater Suzhou Area and the immediate surrounding region in southern China. On average there are 25,000 children admitted each year including on average 600 PICU admissions. In 2006, there were 8.26 million people in Suzhou itself with a pediatric population (0–14 years) of 1.2 million in 2006. By 2010, the population in Suzhou had risen to 13 million with a pediatric population of 1.5 million.

To be eligible for participation in the study, the child needed to be aged 1 month up to 14 years of age, be admitted with community acquired pneumonia to the PICU within 24 hr of hospitalization and have met the World Health Organization criteria for severe or very severe pneumonia.[8] Children with co-morbidities such as meningitis, chronic respiratory diseases or infection with pandemic H1N1 influenza were excluded.

All children with pneumonia in the PICU were managed in a standard manner by protocol. This included on PICU admission verification of the history, a general physical examination with particular focus on chest examination, a chest X-ray, a complete blood count, blood culture, serum electrolytes, arterial blood gas analysis, liver and renal function tests and nasopharyngeal aspirates for detection of respiratory syncytial virus, adenovirus, influenza virus and parainfluenza virus using direct immuno-fluorescence assays (Chemicon International, Inc., Temecula, CA). Deep endotracheal aspirates, if the child was intubated, were sent for routine bacterial culture. For detection of *Mycobacterium tuberculosis,* in selected cases where there was a history of night sweats, poor nutrition, and afternoon tidal fevers, gastric aspirates and/or sputum were sent for smear and culture. Paired serum samples were taken 2 weeks apart for testing for *Mycoplasma pneumoniae* using specific MP-IgM, IgG antibodies measured by quantitative ELISA (Serion Immundiagnostica & Institut Virion\Serion GmbH, Germany). Other laboratory and imaging investigations included chest magnetic resonance imaging if extensive consolidation on routine chest film, assessment of coagulation and other factors when clinically indicated. All children routinely received antibiotics on admission to the PICU.

Criteria for assisted ventilation was patterned after guidelines from South Africa[9] and included the following: (i) failure to maintain a saturation of >90% on an FIO2 of >70% (i.e., on a poly mask); or if the partial pressure of arterial oxygen (PaO2):FIO2 ratio is <100 (normal is 350); (ii) apnea; (iii) hypercarbia with resulting acidemia (pH < 7.25); and/or (iv) clinical assessment of impending exhaustion due to ongoing high respiratory rate and/or severe chest-wall indrawing.

All demographic and laboratory data were collected in a systematic manner.

Statistical Analysis

All statistical analyses were done using SPSS 13.0 software. The χ^2 test or Fisher's exact test was used to compare categorical variables between fatal and non-fatal cases, cases requiring mechanical ventilation versus not and those with prolonged PICU stay. Abnormal laboratory findings were compared by rank test. Univariate analyses were done to determine risk factors significantly associated with severity of CAP in the PICU. To determine the independent contribution of each factor towards case outcomes, multiple logistic regression analysis was done. $P < 0.05$ was considered statistically significant.

Funding, Ethical Approval, and Consent

The study was approved by the Research Ethics Board of the Children's Hospital affiliated with

Soochow University. Written informed consent was obtained from all subject's parents before study enrollment. Funding came from Soochow University.

RESULTS

Over the 4 year period, 10,836 children within the eligible age range were admitted to the hospital with community acquired pneumonia (CAP). Of these, 810 (7%) met eligibility criteria for admission to the PICU. Of the 810 admitted to the PICU, 103 (13%) were not enrolled. Of these 103 cases, 76 cases were excluded because parents refused consent and 27 because of other criteria; 23 with pH1N1, 2 with underlying bacterial meningitis and 2 with underlying chronic respiratory diseases. Of the 707 who were enrolled, 671 (95%) were directly admitted to PICU and 36 were transferred from the ward within 24 hr of hospital admission. All had received antibiotics prior to admission to the PICU. All had been breast fed; for older children at least for 1 year.

Of note none had received influenza vaccine, conjugated pneumococcal or *Haemophilus influenzae* b vaccines as this is not part of routine care in China but all had received BCG vaccine.

The demographics are shown in Table 1. Of the 707 patients, 63% (446/707) were male; gender ratio 1.7 to 1. The mean age was 4 months (range, 1–180 months) with 76% (535/707) under <12 months of age. None were over 5 years of age. The average length of stay in PICU for CAP was 5 days (range, 3–27 days). The CAP PICU case fatality rate was 5.8% (41/707).

TABLE 1— Demographics and Outcome of the 707 Children With Severe Community Acquired Pneumonia Admitted PICU

Age–mean in months	Number, N (% or range)
Median 4 range (1,120)	
1 m	93 (13)
2 m	158 (22)
3 m	80 (11)
4 m	5 (1)
5 m	34 (5)
6–12 m	165 (23)
>12 m ⩽ 24 m	50 (7)
>24 m	71 (10)
Gender, % male	446 (63)
Outcome	
Number that needed oxygen	707 (100)
Number that required Mechanical ventilation	151 (21)
Length of mechanical ventilation (days)	7 (2, 22)
Length of PICU stay (days)	7 (4, 25)
Death	41 (6)

In 235 (31%), an underlying co-morbid condition was present (Table 2). Underlying congenital heart disease was most common (147/235(63%)) with 66 (45%) having a ventricular septal defect, 36 (24%) an atrial septal defect and another 37(25%) both atrial and ventricular septal defects. Only 8 (5%) had cyanotic heart disease. In 205 (91%) of those with an underlying condition, this diagnosis was known prior to admission for severe CAP. However, 28 children with congenital heart disease (19%) and two with immunodeficiency were diagnosed during the PICU admission.

Presenting abnormal clinical and laboratory findings on admission to the PICU are shown in Table 3. All had cough and retractions and 79% (558) had fever over 38°C rectally. Severe respiratory distress, lethargy or decreased level of consciousness were uncommon with each found in only 10% but diarrhea was present in 210 (30%) on admission. In 86% (608/707) of the children, chest radiograph showed consolidation or significant infiltrates on admission to the PICU. In the rest, the findings were increased pulmonary markings and/or small infiltrates. In 136 (19%) magnetic resonance imaging of the chest was also done; all had consolidation or infiltrates but 13 (2%) also had pleural effusions and thickened pleura.

Overall, 21% (151/707) required mechanical ventilation. Significant factors predictive of respiratory failure on admission were abnormal respiratory findings such as head nodding, grunting, cyanosis, respiratory rate over 70/min as well as anemia on single factor analysis (all $P < 0.05$; Table 3). A total of 458/707 (65%) stayed in the PICU for more than 5 days (Table 3). When the 41 fatal cases were compared to the 666 survivors on single factor analysis, admission respiratory rate >70/min, grunting/groaning, cyanosis, oxygen saturation <90% at arrival and hemoglobin <8 g/dl were each associated (all $P < 0.05$; Table 3). Laboratory findings associated with fatality were abnormal glucose either high or low (>6.2 mmol/L, <2.5 mmol/L), CK-MB(>26 U/L)and lactate dehydrogenase(LDH >382 U/L; all $P < 0.05$; Table 3).

A causative agent was detected in 61% of the cases with viral agents predominating over bacteria 38% (269/707) versus 23% (162/707; $P < 0.001$; Table 4). Of the viral causes, respiratory syncytial virus was most common, that is, 63% of the 255 with similar rates in those with congenital heart disease versus those with no co-morbidity (57% vs. 61% $P > 0.05$). *Mycoplasma* was the most common bacterial pathogen accounting for 11% of total cases but 47% of those in whom bacteria was detected. Blood cultures were positive in only 5, that is, 0.7%; two with *Streptococcus pneumoniae*, two with *Haemophilus influenzae* b and one with *Staphylococcus aureus*. In two others, the isolated bacteria was thought to be contaminates: *Bacillus* species,

TABLE 2— Underlying Conditions in Children Admitted With Severe Community Acquired Pneumonia in the PICU

Co-morbid conditions, N = 235 (33% total)	Diagnosis: known prior to PICU admission	Diagnosis: during PICU admission
Congenital heart disease no Trisomy 21 syndrome	109	28
Congenital heart disease and Trisomy 21 syndrome	10	0
Trisomy 21 syndrome	25	0
Cerebral palsy or other neurodevelopmental condition	25	0
Premature birth (<37 weeks)	18	0
Malnutrition	15	0
Immune deficiency	5	2

coagulase negative *Staphyloccocus*. In nine children, tuberculosis was diagnosed based upon positive gastric aspirate or sputum smears for *M. tuberculosis.* Of the six children with pleural fluid cultures, four were negative; one grew *Streptococcus pneumoniae* and one *Staphylococcus aureus.* Both of these also had positive blood cultures. Concurrent viral and bacterial infection did occur but was not more frequently with *S. pneumoniae* than with *Haemophilus influenzae* b cases (20% vs.12%, $P > 0.05$). No patient with *Mycoplasma* had a concurrent viral infection detected.

On multivariate analysis, underlying factors associated with prolonged PICU stay included young age, presence of congenital heart disease or cerebral palsy (Table 5A). Fatality was associated with congenital heart disease, Trisomy 21 syndrome, cerebral palsy, and immune deficiency (Table 5B). No relationship was noted between fatality and specific pathogens, laboratory admission or clinical findings on multivariate analysis.

DISCUSSION

Severe pneumonia requiring an admission to the PICU represented 7% of all CAP admissions over the 4 years of this prospective study in south China. Very severe CAP occurred most frequently in those under 1 year of age (76%) and one third had underlying or co-morbid conditions with 21% having congenital heart disease. In 30% of these, the co-morbid condition was not known prior to PICU admission. The fatality rate was 5.8%. On single factor analysis, PICU admission respiratory rate >70/min, grunting/groaning, head nodding,

TABLE 3— Risk Factors in PICU Admission for Severe Community Acquired Pneumonia in PICU in Suzhou in China

Characteristics	Children	Children needing prolonged PICU stay		Children needing mechanical ventilation		Outcome	
Number	N = 707 (%)	Yes, N = 458 (%)	No, N = 249 (%)	Yes, N = 151 (%)	No, N = 556 (%)	Fatal, N = 41 (%)	Non-fatal, N = 666 (%)
Age < 12 months	586 (83)	370 (81)	216 (87)	98 (65)	350 (63)	34 (83)	503 (76)
Sex: males	446 (63)	297 (65)	149 (60)	97 (64)	349 (63)	30 (73)	416 (62)
Altered sensorium	219 (31)	167 (36)	52 (21)	68 (45)	151 (27)	38 (93)	181(27)*
Respiratory rate >70/min	395 (51)	316 (69)	79 (32)*	143 (95)	252 (45)*	39 (95)	356 (53)*
Wheezing	256 (36)	87 (19)	169 (68)*	8 (5)	248 (45)*	1 (2)	255 (38)*
Grunting/groaning	398 (56)	348 (76)	50 (20)*	135 (89)	263 (47)*	40 (98)	358 (54)*
Head nodding	152 (21)	130 (28)	22 (9)	89 (59)	63 (11)*	31 (76)	121 (18)*
Cyanosis	289 (41)	241 (53)	48 (19)*	109 (72)	180 (32)*	37 (90)	252 (38)*
Pallor	135 (19)	101 (22)	34 (14)	32 (21)	102 (18)	31 (76)	104 (16)
Oxygen saturation <90% at arrival	318 (45)	287 (63)	31 (12)*	113 (75)	205 (37)*	38 (93)	280 (42)*
Hemoglobin <8 g/dL	80 (11)	67 (15)	13 (5)	63 (42)	17 (3)*	25 (61)	55 (8)*
Abnormal Leukocyte count, (per mm^3) low: <4,000 or high > 10,000	360 (51)	312 (68)	45 (18)*	98 (65)	349 (63)	19 (46)	338/653 (52)
Abnormal Glucose (>6.2 mmol/L, <2.5 mmol/L)	452 (64)	271 (59)	160 (64)	87 (58)	344 (62)	39 (5)	394/639 (56)*
Creatine kinase >225 (U/L)	282 (40)	173 (38)	128 (51)	80 (53)	221 (40)	16 (39)	285/666 (43)
Creatine kinase-MB fraction (>26 U/L)	286 (40)	192 (42)	103 (41)	76 (50)	219 (39)	26 (63)	272/599 (45)*
Lactate dehydrogenase >382 (U/L)	395 (56)	251 (55)	105 (42)	81 (54)	275 (49)	30 (73)	329/607 (54)*
Cr > 84 (μmol/L)	7 (1)	5 (1)	2 (1)	2 (1)	5 (1)	1 (2)	6/666 (1)
Aspartate aminotransferase >67 (U/L)	177 (25)	105 (23)	53 (21)	36 (24)	122 (22)	13 (32)	147/600 (25)
Alanine aminotransferase >35 (U/L)	198 (28)	142 (31)	22 (13)	44 (29)	131 (24)	10 (24)	166/600 (28)
C-reactive protein >8 (mg/L)	247 (35)	153 (33)	68 (27)	57 (38)	154 (29)	20 (49)	204/602 (34)

*$P < 0.05$.

TABLE 4— Pathogens Detected With Children With and Without Underlying Conditions With Severe Community Acquired Pneumonia

		Viral pathogen			Bacterial pathogen				
Underlying condition	No pathogen detected	RSV	Influenza	Other[1]	*S. pneumo*	*Staph aureus*	*M. tb*	*Hib*	*M. pneum*
None (505)	193[2]	131	40	31	30	0	5	20	55
CHD (137)	59	25	10	9	10	0	2	7	15
CHD with T21 (10)	4	1	1	1	1	0	0	1	1
T21 (25)	10	8	2	1	2	0	0	1	1
ND (25)	10	4	2	0	1	1	1	1	3
ID (7)	0	2	1	0	2	0	1	0	1
Total	278 (39%)	171 (24%)	56 (8%)	42 (6%)	46 (7%)	1 (<1%)	9 (1%)	30 (4%)	76 (11%)

S. pneumo, *Streptococcus pneumoniae; Staph aureus*, *Staphylococcus aureus; M. tb*, *Mycobacterium tuberculosis; Hib*, *Haemophilus influenzae* b; *M. pneum*, *Mycoplasma pneumoniae*.
[1]Other viruses = parainfluenza and adenoviruses.
[2]Ten children had either *S. pneumoniae(5)* or *H. influenza b(5)* isolated from nasopharyngeal aspirates but as this can be part of normal nasopharyngeal flora they were excluded in the totals for bacterial pathogens. None of the 10 had an underlying condition.

cyanosis, oxygen saturation <90% and hemoglobin <8 g/dl were each associated with fatality but and on multivariate analysis only the presence of congenital heart disease, Trisomy 21 and immunodeficiency correlated. Neither specific pathogens, nor admission laboratory or presenting clinical findings correlated.

While there are no comparable large cohort studies of very severe CAP being managed in PICU settings in China, India or another developing country, previous reports on CAP or acute lower respiratory infections in children in developing countries have emphasized young age, late hospitalization, changes in sensorium, grunting, head nodding, inability to drink, loose stools, presence of bacteremia, heart disease, anemia, rickets, and lack of breast feeding as predisposing factors for fatality.[10–19] This large PICU cohort study from China provides corroboration for changes in sensorium, high respiratory rate >70/min, grunting/groaning, head nodding and cyanosis as significant clinical predictive factors of fatality on univariate analysis. The major importance of young age noted here and in other studies must not be overlooked.

A number of the factors associated with fatality highlighted in earlier studies noted above were not seen in this PICU cohort study. In part, this may have been because some have been addressed at the population level. For example, no child in this PICU cohort had rickets because vitamin D supplements are routinely given in this area in China. In contrast, rickets was a major associated factor in fatalities in the earlier reports from Yehman.[13,14] Breast feeding is universal in the first year in this region in China so could not be evaluated as an associated risk factor. Bacteremia was detected rarely in this PICU cohort (0.7%) possibly because all had received antibiotics prior to admission to the PICU, even the ones admitted directly to the PICU. Two more recent studies, one from India[18] with 200 children reported in 2007 and the other from the

TABLE 5— Risk Factors for Length of Stay and Fatality in PICU for Severe Community Acquired Pneumonia in PICU by Multivariate Analysis

						RR 95%CI	
Variables	β	SE	Waldχ^2	*P*	OR	Lower	Upper
Risk factors for length of stay							
Age	−0.091	0.041	4.837	0.028	0.913	0.843	0.990
Congenital heart disease	0.857	0.213	16.177	0.000	2.357	1.552	3.580
Cerebral palsy	1.360	0.491	7.6667	0.006	3.896	1.488	10.203
Constant	−1.174	0.198	35.266	0.000	0.309		
Risk factors for fatality							
Congenital heart disease	1.838	0.367	25.009	0.000	6.281	3.057	12.906
Down syndrome	1.920	0.523	13.462	0.000	6.823	2.446	19.032
Cerebral palsy	2.162	0.692	9.763	0.002	8.693	2.239	33.750
Immune deficiency	4.177	0.955	19.127	0.000	65.196	10.027	423.895
Constant	−3.772	0.281	180.082	0.000	0.023		

Philippines[19] with 1,249 children also reported in 2007 have noted the importance of bacteremia (15% and 2.6% respectively). The fatality rate in the study in India was higher than in our PICU cohort (10.5% vs. 5.8%, $P < 0.03$); but the rate in the very large study from the Philippines was lower (2.6% vs. 5.8%, $P < 0.03$). However as noted, both of these studies included all children admitted with CAP while ours only included those admitted to PICU making the interpretation of differences more difficult.

The importance of underlying conditions is also noteworthy. In this PICU cohort, 21% had congenital heart disease and in slightly more than one quarter the diagnosis was not made until the child was in the PICU. While 127 of the 200 children in the 2007 Indian CAP study had ''no evidence of congenital heart disease,'' the actual number with confirmed congenital heart disease is not stated so comparison is not possible. The study from the Philippines also does not specify.

In developing countries with meager resources, care provided by primary village health teams who have received brief and modest training in basic care and appropriate referrals to district health centers has been shown to decrease mortality in the under 5 years age group[20] but ready access to tertiary care with a PICU is unlikely in such settings. However, in developing countries with more resources such as Bangladesh, Thailand, and Pakistan who have also used the community health worker model with good outcomes,[21] being able to prioritize early those likely in need of the aggressive support available in a PICU might well improve CAP outcomes. Having these community health workers taught how to recognize pneumonia, treat early with simple antibiotics and then refer urgently if signs such as nodding, altered sensorium and/or grunting are present might facilitate more timely presentation to major centers where additional care options such as assisted ventilation in a PICU is possible.

With respect to microbial causes, the relatively high rate of pneumococal and *Haemophilus influenzae* b infections in this age group is not surprising given that China does not routinely use the vaccines that cover for either. The bacterial cases may well have been underestimated because as noted above all had received antibiotics prior to the blood or endotracheal cultures being collected. A 2009 case control study from Brazil suggests that *Haemophilus influenzae* b vaccine could prevent an estimated 30% of hospitalized cases of radiologically definite CAP in children under 2 years of age.[22] Our earlier prospective study of children hospitalized with CAP in Northwest China also noted *H. influenzae* b and *S. pneumoniae* as relatively common pathogens.[23] Of note, the World Health Organization *Global Action Plan For Prevention and Control of Pnuemonia* in 2008 listed immunization coverage for *S. pneumoniae* and *H. influenzae* b as well as immunization against measles and pertussis as top prevention strategies.[2] This PICU study from China supports the observation from Thailand that *Mycoplasma* is an important pathogen in children in developing countries hospitalized with CAP including those aged 2–5 years[24] and extends it to include those with CAP in the PICU. *Mycoplasma* was the most common bacterial pathogen detected, found in 11% overall and 47% of those with a bacterial pathogen. No child in this PICU cohort was over 5 years of age.

Respiratory syncytial virus is a well recognized cause of severe respiratory disease in both industrialized as well as developing countries[25,17,26,27] particularly in those with underlying conditions such as congenital heart disease.[28] In our PICU CAP cohort, respiratory syncytial virus was detected in 23% of the cases and 64% of those in which a virus was found. Twenty percent of those with respiratory syncytial virus also had congenital heart disease. In our previous study of CAP in children hospitalized in northwest China,[23] respiratory syncytial virus accounted for 42% of the viral cases and 18% of cases overall.

The impact of influenza may have been underestimated in this PICU CAP cohort in China as pandemic H1N1 cases were excluded from the study as they were felt to be unrepresentative of influenza and hence a year of influenza PICU cases were excluded. Others have noted the importance of non-pandemic influenza in CAP in developing countries.[26,27] We were not able to corroborate the observation in an industrialized country setting (United States) that children in a PICU with non-pandemic community acquired influenza with bacterial pneumonia were at marked increase risk for respiratory failure compared to those without bacterial pneumonia.[29] This association may not have been seen because of our low numbers of influenza cases (56, 8%) and relatively low rate of bacteremia rate (0.7%).

We were also unable to validate the Bacterial Pneumonia Score developed in Argentina to help distinguish in children with viral from bacterial pneumonia.[30] Given that this score was developed for application on CAP admission to hospital and focuses on axillary temperature, white count, percentage of bands and chest radiograph findings, it is not surprising that in children with CAP severe enough to warrant PICU care there might not be as much difference in these factors.

There are other limitations to our study. As noted above, the importance of both common bacteria and influenza may have been underestimated; the former because of antibiotic use prior to cultures being taken and the latter because of exclusion of all pH1N1 cases as unrepresentative. As well the overall repertoire of microbes tested for was limited. Due to cost constraints, neither rhinovirus, human bocavirus, human

metapneumovirus, human coronavirus nor *Moraxella catarrhalis* were tested for although all have been reported in varying rates in children hospitalized with acute respiratory tract infections including CAP[31–36] including two viral studies in China.[34–36] Potential contributing community and family factors were also not examined in our study as this information was not collected. Assessment of factors such as overcrowding and air pollution might be helpful to see if these apply in the PICU CAP patients in the same manner as in children hospitalized with CAP.[18,37]

In conclusion, this large cohort study of children with very severe CAP in China has confirmed in a developing country the importance of young age and underlying factors such as congenital heart disease in the most severe cases, that is, those needing PICU support. This study provides yet more evidence on the importance of universal immunization with vaccines against *S. pneumoniae* and *H. influenzae* b as recommended by the World Health Organization. Even access to quality PICU support cannot overcome the serious morbidity associated with these bacteria. Prevention is a better option. Countries with emerging economies like India and China need to move forward to provide these two vaccines to all of their children. Beyond this prevention strategy, given the very large numbers of children in China and India and the increasing access to PICUs in many regions early recognition and referral of severe cases may also help to decrease fatalities. More studies are needed to hone best practices for managing pneumonia coming from the community in different developing country settings. This further confirmation that altered sensorium, head nodding and grunting are markers for increased fatality raises the question of whether more training on these markers at the community health worker level can increase recognition and speed of referral for highest risk cases to centers with PICUs.

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