

Original Article

Clinical report of serious complications associated with measles pneumonia in children hospitalized at Shengjing hospital, ChinaJiujun Li¹, Ying Zhao¹, Zhe Liu¹, Tao Zhang¹, Chunfeng Liu¹, Xin Liu²¹ Department of Pediatrics, Shengjing hospital of China Medical University, Shenyang, China² Department of Radiology, Shengjing hospital of China Medical University, Shenyang, China**Abstract**

Introduction: Despite tremendous progress made toward elimination, measles continues to pose a great threat to the health of children in developing countries. The objective of this study was to summarize and analyze the clinical characteristics and treatment experience of serious complications of measles pneumonia in children.

Methodology: The study group comprised 58 infants with severe measles pneumonia who were admitted to the Second Pediatric Intensive Care Unit, Shengjing Hospital of China Medical University, from December 2013 through May 2014. The clinical characteristics of complications such as hypoxemia, acute respiratory distress syndrome (ARDS), sepsis, pneumothorax, multiple organ dysfunction syndrome (MODS), and intracranial infection were retrospectively analyzed; in addition, the death cases were summarized and analyzed.

Results: The 58 infants experienced the following: hypoxemia, 100%; ARDS, 21%; sepsis, 34%; pneumothorax, 14%; MODS, 16%; and intracranial infection, 9%. A total of 7 infants developed a secondary bacterial infection, and 12 infants received mechanical ventilation (5 with high-frequency mechanical ventilation and 3 with mechanical ventilation and NO inhalation); the average duration of mechanical ventilation was 10.08 days, and 3 infants expired.

Conclusions: Children with measles pneumonia may experience multiple serious complications, among which ARDS and pneumothorax are particularly serious. If a patient's condition changes abruptly, it is crucial to promptly respond to the change and to administer mechanical ventilation and appropriate antibiotics. For patients with a severe pneumothorax, and especially those with severe mediastinal emphysema, timely, continuous, retrosternal, closed thoracic drainage can effectively relieve compression.

Key words: measles; pneumonia; complications; infant.

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Introduction

Measles is a highly contagious respiratory infection with a significant transmission risk. It was once thought to be on the verge of elimination; however, outbreaks in Europe have resulted in a resurgence. Despite this resurgence, however, experience with measles is limited [1]. Annually, worldwide, approximately 45 million new measles cases occur and nearly one million individuals die of measles. Most of the victims are children in developing nations. Measles remains the major cause of global childhood deaths. In 2000, the World Health Organization (WHO) estimated that 1.7 million children died of vaccine-preventable diseases in the world, and among them, 777,000 (46%) children died of measles [2]. In May 2005, the WHO/United Nations International Children's Emergency Fund (UNICEF) Global Immunization Vision and Strategy (GIVS) (WHO/UNICEF-GIVS) was passed at the 58th World

Health Assembly (WHA). According to the treaty, all concerned nations were given the goal to decrease the global mortality of measles by 90% by 2010. In 2010, the goal of achieving three milestones by 2015 was passed at the WHA [3]. In recent years, measles has exhibited an increasing epidemic trend in China. Based on the data from the Chinese Center for Disease Control and Prevention (CDC), 7,663 cases of measles were reported nationwide in the first ten weeks of 2014, showing a growth of 59.7% compared with the same period of 2013 (4,802 cases). Today, measles is still seriously threatening the health and life of children; thus, it attracts global concern. After acquiring measles, children often die as a result of complications rather than from measles itself. Pneumonia is the most common cause of death related to measles; mortality is relatively high in patients with severe pneumonia. We reviewed the clinical case data of 58 infants with severe measles pneumonia who

were admitted to the second pediatric intensive care unit (PICU), Shengjing Hospital of China Medical University.

Methodology

General data

The study group comprised 58 infants (44 males and 14 females) with severe measles pneumonia who were admitted to the 2nd PICU, Shengjing Hospital of China Medical University from December 2013 through May 2014. The average patient age was 10.5 months (range: 2 months to 4 years). Eleven cases were over one year of age, and the others were one year of age or younger; most were five to eight months of age. Fifty-five of the infants were not inoculated with measles inactivated live vaccine, and only three infants were inoculated with that vaccine. Eleven cases had a definite history of contact with measles. Seventeen cases were permanent urban residents, and the others were permanent rural residents. With regard to underlying diseases, two infants had cerebral palsy, two infants had moderate anemia, and three infants had congenital heart disease (one had primary tracheal stenosis).

At admission to the PICU, all 58 patients had pneumonia and hypoxemia. Twelve had acute respiratory distress syndrome (ARDS) and received mechanical ventilation; of these, five were treated with high-frequency mechanical ventilation, and the others were treated with conventional mechanical ventilation. Among the five who were treated with high-frequency mechanical ventilation, three were treated with NO inhalation. Eight patients had a pneumothorax or mediastinal and subcutaneous emphysema. Nine patients had multiple organ dysfunction syndrome (MODS). Four patients had encephalitis. Twenty-three patients were septic, but none had septic shock. Eighteen patients had an upper gastrointestinal stress ulcer.

Of the 58 patients, three expired (5%). One infant suffered respiratory arrest and mydriasis at admission due to pre-hospital asphyxia; the infant was pronounced dead after 4.5 hours of resuscitation efforts.

Diagnostic criteria

Diagnostic criteria of measles pneumonia [4] included (1) clinical diagnosis in a child with all of the following: generalized maculopapular rash lasting more than three days, temperature > 38°C, and cough with coryza or conjunctivitis; (2) serologic (IgM antibody) confirmation of the disease; or (3)

pneumonia confirmed by clinical manifestations and imaging.

Diagnostic criteria of ARDS were the Berlin criteria 2012 [5].

Diagnostic criteria of sepsis were those jointly developed by the American Thoracic Society/American Society of Critical Care Medicine in 2005 [6].

Diagnostic criteria of MODS were the Chinese diagnostic criteria of child MODS [7].

Methods

Statistical analyses were performed on the complications of all 58 measles pneumonia patients, including hypoxemia, ARDS, sepsis, pneumothorax, and MODS. The following parameters were analyzed: number of patients with each complication, time from disease onset to admission, average PICU stay, average hospital stay, number of cases on mechanical ventilation, mechanical ventilation time, as well as incidence rate and clinical characteristics of each complication. The cases with bacterial infection and death-related factors of the three cases of death were analyzed.

Treatment of hypoxemia included oxygen inhalation, sedation, glucocorticosteroid inhalation, bronchodilators, and anti-inflammatory, symptomatic, and systematic support therapy. Treatment of sepsis and MODS included anti-infection measures, maintenance of vital organ function, fluid and electrolyte maintenance, caloric intake maintenance, and systemic support therapy. Treatment of ARDS included mechanical ventilation, or high-frequency mechanical ventilation plus NO inhalation when conventional mechanical ventilation was inadequate. Subcutaneous or mediastinal emphysema required prompt treatment by immediate subcutaneous fasciotomy and continuous closed thoracic drainage. For patients with a severe pneumothorax, especially those with severe mediastinal emphysema, continuous retrosternal closed thoracic drainage is required. In the presence of symptoms of an intracranial infection, sedation, anticonvulsant therapy, intracranial pressure reduction, and neuroprotective head sub-hypothermia is indicated.

Results

Analysis of complications

At PICU admission, all 58 measles pneumonia patients had different degrees of hypoxemia, and 47 had significant hypoxemia plus cough with asthma. Twelve infants rapidly progressed to ARDS within

two days of admission to PICU. At PICU admission, eight cases presented with different degrees of pneumothorax, and six had severe mediastinal emphysema and pneumothorax, which required closed thoracic drainage plus mechanical ventilation. Two infants achieved significant improvement in their condition after incision of the subcutaneous emphysema and institution of closed thoracic drainage; these infants did not require mechanical ventilation. Twenty-three infants had sepsis manifestations; however, none developed septic shock. Nine infants experienced MODS due to lung disease aggravation and hypoxemia, primarily manifesting as liver dysfunction, myocardial damage, disseminated intravascular coagulation (DIC), and an upper gastrointestinal stress ulcer. Four infants presented with symptoms of central nervous system involvement, predominantly manifested by convulsions and decreased consciousness within three days of admission; they were diagnosed with an intracranial infection with the aid of a lumbar puncture and cerebrospinal fluid (CSF) examination, 24-hour active electroencephalogram (EEG), and head magnetic resonance imaging (MRI). Two infants with convulsions during the course of the disease were ultimately diagnosed with febrile seizures and epilepsy (Table 1).

Analysis of bacterial infection complications

Of the 58 measles patients, seven suffered bacterial or fungal infections with corresponding clinical symptoms; the repeat bacterial culture of sputum aspirated by deep tracheal intubation showed the same strain, but no infant had a positive blood culture result. All seven infants developed bacterial infections 48 hours after admission, which persisted for 2–13 days. Before admission, they had received treatment for 5–8 days in other hospitals. The

pathogenic bacteria were primarily *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*; the pathogenic fungus was *Candida albicans* (Table 2).

Analysis of death cases

Three of the 58 measles patients expired. One patient with measles and laryngitis experienced bucking and asphyxia after a milk feeding at home. The infant presented with respiratory and cardiac arrest and mydriasis at admission, and was finally pronounced clinically dead after 4.5 hours of resuscitation efforts. The other two infants with serious pulmonary inflammation progressed to ARDS and pneumothorax. Despite mechanical ventilation, NO inhalation, and closed thoracic drainage, the patients expired (Table 3).

Discussion

Measles is an acute infectious disease caused by the measles virus; it has strong infectivity and is common in children. Patients in the acute phase are the unique source of infection. Following close contact with a measles patient, more than 90% of susceptible individuals will develop measles. Populations who have no history of measles and who have never been inoculated with measles vaccine, or who were once inoculated with measles vaccine but currently have a low antibody levels, have inadequate immunity to the measles virus. In this study, only three infants were inoculated with measles inactivated live vaccine; the other 55 were not. Most of the infants were between five and eight months of age; eleven had a definite history of contact with measles; seven had other underlying diseases; and five were critically ill and experienced ARDS, which necessitated mechanical ventilation. In addition, the critical cases primarily occurred in April and May.

Table 1. Clinical data of 58 measles patients with complications

	N (%)	Age (months)	Sex ratio (M/F)	Time from onset to admission (days)	Average PICU stay (days)	Average hospital stay (days)	Number of cases on mechanical ventilation (%)	Mechanical ventilation time (days)
Hypoxemia	58 (100)	2–48 (10.51)	44/14	3–16 (6.58)	14.13	15.8	12 (20.69)	1–23 (10.08)
ARDS	12 (20.69)	5–48 (15)	10/2	5–16 (7.82)	23.92	24.67	12 (100)	1–23 (10.08)
Sepsis	23 (39.66)	2–48 (12.13)	17/6	5–16 (6.91)	18.78	19.96	11 (47.82)	1–23 (10.36)
Lung air leakage	8 (13.79)	5–48 (8.125)	6/2	5–16 (8.12)	25.5	26.88	6 (75)	4–23 (12.83)
MODS	9 (15.52)	5–48 (16.56)	7/2	5–16 (8.11)	25.11	26	9 (100)	5–48 (11.44)
Intracranial infection	4 (8.62)	3–48 (25)	2/2	2–7 (5.5)	20.75	23.25	1 (25)	14 (14)

PICU: pediatric intensive care unit; ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome

Table 2. Clinical data of bacterial infection patients

No.	Sex	Age (months)	Time from onset to admission (days)	Time from admission to infection (days)	Time from mechanical ventilation to infection (days)	Hospital stay (days)	Sample type	Bacterium type	WBC at infection ($\times 10^9/L$)	CRP (mg/L)	PCT (ng/mL)
	M	9	7	5	2	31	Sputum	<i>Acinetobacter baumannii</i> , <i>Klebsiella pneumoniae</i>	27.8	14.6	0.358
2	M	5	7	2	1	23	Sputum	<i>Acinetobacter baumannii</i> , <i>Klebsiella pneumoniae</i>	27.7	77.1	1.15
3	F	48	7	6	6	34	Sputum	<i>Pseudomonas aeruginosa</i>	25.9	33	8.97
4	M	30	8	5	5	29	Tracheal intubation/urinary catheter	<i>Acinetobacter baumannii</i> / <i>Candida albicans</i>	12.2	110	2.59
5	M	14	5	13	9	59	Sputum	<i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i>	14.6	49.0	20.77
6	M	10	5	8	7	22	Sputum	Two Gram-positive cocci, two Gram-negative bacilli	31.7	< 3.450	0.23
7	M	23	6	7	12	22	Sputum	<i>Candida albicans</i>	13.3	32.4	0.296
Mean		23	6.3	6.7	6	31.43					

Table 3. Clinical data of death cases

No.	Sex	Age (months)	Time from onset to admission (days)	Time from admission to death (days)	Root cause of death	Special history
1	Male	30	8	30	ARDS, air leakage, MODS	Growth retardation
2	Female	8	16	11	ARDS, air leakage, MODS	Gestational weeks: 29 weeks + 5 days, the smaller twin had epilepsy
3	Male	6	10	4.5 hours	Asphyxia, MODS	Pre-hospital asphyxia, cyanosis of lips for 3.5 hours

ARDS: acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome

Measles patients often recover without sequelae; however, serious complications may develop. Measles pneumonia is one of the most common complications and is frequently seen in infants and patients with compromised immune systems. Measles pneumonia is also the most common cause of death in infants with measles, and those infants with pneumonia and serious complications have a higher mortality [8-9]. In most cases of pneumonia caused by measles, the infection is viral interstitial pneumonia. In addition to interstitial tissue damage, most severe measles pneumonia cases have congestion, edema, and even necrosis and exfoliation of bronchial and bronchiolar mucosa. As an increase of respiratory inflammatory secretions produces transient hypimmunity, these patients will readily suffer from other viral or bacterial infections, leading to an increase in the incidence rate of severe pneumonia, and even inducing acute lung injury or ARDS. The pathogenesis may be associated with secondary severe pneumonia and systematic infection, as well as a systematic inflammatory reaction syndrome (SIRS) induced by the release of large amounts of *in vivo* inflammatory factors such as surfactant protein D (SP-D) and interleukin-6 (IL-6); damage to pulmonary capillary basement membranes and epithelial cells can also occur [10].

Measles pneumonia is caused by a viral infection, but young infants often suffer from secondary infections by other pathogenic bacteria because of airway obstruction caused by airway mucosal edema after such an infection. This is why some infants with measles pneumonia have sepsis and significant increases in their white blood cell count (WBC) and C-reactive protein (CRP) or pre-calcitonin (PCT). If not treated promptly, these patients have a high mortality rate. Shen *et al.* [11] reported that, by monitoring the changes of WBC and CRP levels in infants with measles, it was possible to identify the complication of bacterial pneumonia at an early stage. According to Xu *et al.* [12], 2 of 22 cases of severe measles pneumonia developed septic shock. One patient had a severe bacterial infection and empyema with septic shock at admission; subsequently, ARDS developed, and the blood culture and pleural fluid culture both indicated *Streptococcus pneumoniae*. In this study, 23 infants had sepsis manifestations with a significant increase in WBC, CRP and PCT; however, none developed septic shock. This finding was likely attributable to the timely pre-hospital treatment and the use of antibiotics. Secondary bacterial infections usually result in an aggravated case of measles pneumonia. In the present study, seven patients

experienced bacterial or fungal infections with corresponding clinical symptoms at > 48 hours after admission, and the repeated bacterial culture of sputum aspirated by deep tracheal intubation showed the same strain. Increases of WBC, CRP, and/or PCT were also found in most cases. The infections were mainly caused by Gram-negative bacilli such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These infections may be associated with a long pre-hospital treatment time, long-term mechanical ventilation, and the use of broad-spectrum antibiotics. Two cases of a *Candida* infection also recovered after the administration of diflucan. Patients with secondary bacterial infections had longer hospital stays and experienced relapses. Three patients with secondary bacterial infections were hospitalized for one month or longer (max: 59 days; average: 31.4 days).

ARDS is a common critical disorder and also a serious complication of measles. The chest computerized tomography (CT) scans of ARDS patients shows that a large number of pulmonary alveoli collapse and that the lung volume for ventilation is significantly decreased. Therefore, mechanical ventilation tends to cause pulmonary alveolar over-inflation, inducing volutrauma. Mechanical ventilation may result in the periodic collapse and opening of pulmonary alveoli, producing a shearing force, which induces pulmonary alveolar atelectrauma. In addition, the mechanical injury of pulmonary alveoli can activate inflammatory cells and cause the release of inflammatory transmitters, which can induce biological injury [13]. In the 1990s, it was reported that the mortality of measles patients with ARDS or lung consolidation was $\geq 50\%$ [14-15]. At present, the therapeutic strategies for ARDS primarily include the application of mechanical ventilation, lung recruitment maneuvers, fluid management, and the appropriate application of muscle relaxants [16]. In this study, we provided mechanical ventilation for 12 ARDS patients. In five cases, however, basic oxygenation was not maintained even at a high positive end-expiratory pressure (PEEP) after conventional mechanical ventilation; therefore, high-frequency mechanical ventilation plus the appropriate application of muscle relaxants and fluid management were provided. In three cases, NO inhalation was added. Compared with conventional mechanical ventilation, high frequency oscillatory ventilation (HFOV) can be used in patients with intractable hypoxemia, and it is beneficial to achieve the ventilation with a lower tidal volume and a higher

mean airway pressure; this can reduce volutrauma, avoid pulmonary alveolar hyperinflation, maintain pulmonary alveolar recruitment, improve the oxygenation index, and decrease mortality. In addition, there is a very low probability of treatment termination caused by intractable hypoxemia, hypercapnia, hypotension, or barotraumas [17-18]. The primary pathophysiological characteristics of ARDS are hypoxemia and pulmonary hypertension; hypoxemia is attributed to ventilation-perfusion imbalance and increased intrapulmonary shunt. When ARDS occurs, pulmonary vasoconstriction and extensive microvascular occlusion can cause an increase of pulmonary arterial pressure (PAP). In ARDS patients, NO enters the well-ventilated area

after inhalation [19] and then enters the pulmonary circulation in a diffuse form to dilate pulmonary arteries; this improves the ventilation-perfusion imbalance state and the air-exchange function. In addition to relieving hypoxemia, the inhaled NO can decrease PAP and pulmonary capillary pressure (PCP) by dilating pulmonary vessels, improving right heart function, improving the ventilation-perfusion ratio, and promoting the elimination of pneumoedema, thus effectively treating ARDS [20]. In the present study, three patients were provided with high-frequency mechanical ventilation and NO inhalation for severe ARDS after conventional mechanical ventilation proved inadequate. Two of these infants survived and one expired. High-frequency mechanical ventilation plus NO inhalation has good efficacy; therefore, for severe measles pneumonia patients with ARDS and especially patients with pulmonary hypertension, high-frequency mechanical ventilation plus NO inhalation is often the final life-saving measure.

Figure 1. Lung X-ray indicated obvious swelling of the right chest wall, a large number of gas density shadows in right axillary fossa, and mediastinum.

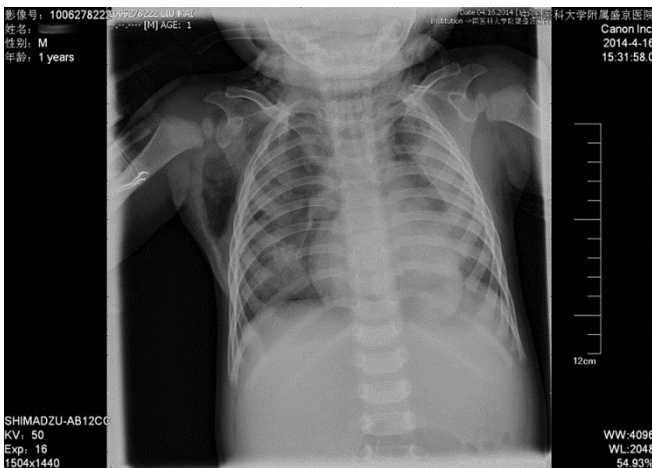


Figure 2. Lung CT indicated a large number of gas density shadows in both anterior superior chest walls and mediastinum, a few gas density shadows in the vertebral canal, free gas density shadows and a visibly compressed lung border in both thoracic cavities and massive high-density patch shadows in both lungs.



Infantile pneumothorax typically has a sudden onset when it is secondary to pulmonary diseases. The lungs of infants are immature; therefore, when pulmonary lesions or other factors cause airway obstruction or stenosis, the air pressure in the alveoli will readily exceed the physiological limit, resulting in alveolar rupture, which in turn results in a pneumothorax as well as mediastinal and subcutaneous emphysema [21]. If a small pneumothorax is discovered and treated promptly, mortality is low. However, the coexistence of ARDS and pneumothorax often indicates a poor prognosis for measles patients. In 1955, Abramson *et al.* [22] showed that all measles patients with ARDS and pneumothorax expired even if they received adequate critical care and airway pressure-limiting treatment. In 2010, Piastra *et al.* [23] reported that two patients with measles ARDS and pneumothorax recovered after treatment. Dong *et al.* [24] analyzed 17 measles patients in the PICU; 6 suffered ARDS and pneumothorax and 4 expired. In this study, 6 of 12 ARDS patients developed mediastinal emphysema or pneumothorax; 4 recovered and 2 expired. When patients develop a pneumothorax, early detection, diagnosis, and treatment are key to successful rescue. Timely implementation of closed, constant thoracic drainage, real-time cardiovascular monitoring of circulation, and timely application of cardiovascular support are all important therapies. In the present study, one ARDS patient suffered serious mediastinal and subcutaneous emphysema as well as minor bilateral subcutaneous emphysema (Figures 1 and 2).

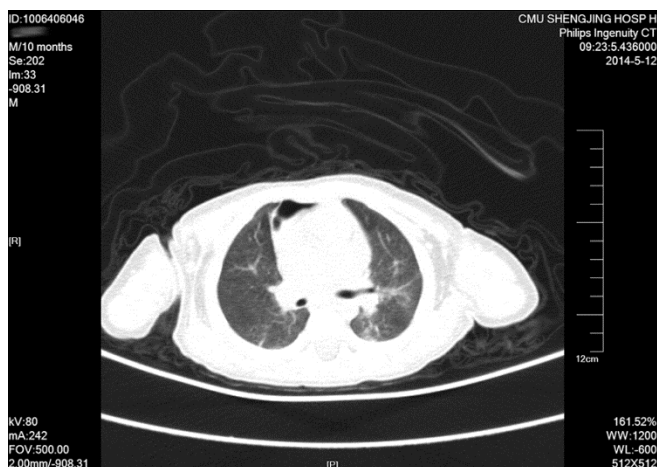
Substernal closed thoracic drainage of the anterior mediastinum was completed under the supervision of pediatric surgeons (Figure 3), and HFOV was provided. After 6 days of mechanical ventilation, the patient was successfully weaned from the ventilator; 17 days later, the drainage tube was removed. A second lung CT before discharge showed that the mediastinal emphysema had completely resolved and the bilateral pneumonia had almost completely cleared (Figure 4). Therefore, for severe pneumothorax patients, and especially those with severe mediastinal emphysema, timely continuous retrosternal closed thoracic drainage can effectively relieve cardiopulmonary compression and prevent death.

Encephalitis is a common complication of measles. It is widely recognized that measles encephalitis is caused by the direct brain invasion of the measles

Figure 3. Substernal closed thoracic drainage in the anterior mediastinum.



Figure 4. CT of lungs in the recovery phase. Bilateral pneumonia had resolved, and only a small amount of free air was present in the superior mediastinum.



virus, and its main CSF findings include an increase of monocytes and protein and a high glucose level. In this study, six patients had central nervous system involvement such as convulsions. With the aid of lumbar puncture, head MRI, and EEG, two were diagnosed with febrile seizures and epilepsy, and four were diagnosed with measles pneumonia and encephalitis. Measles encephalitis usually has a good prognosis. In these four patients, the average hospital stay was 23.23 days, and the symptoms had almost resolved at discharge.

Conclusions

In recent years, measles outbreaks have occurred in several provinces and cities in China. In 2014, the number of measles patients admitted to our hospital increased significantly, and the disease epidemic period obviously lasted more than before. Measles pneumonia patients with serious complications have high mortality. Therefore, it is crucial to promptly and accurately evaluate a change in patient status; when it occurs, appropriate mechanical ventilation, NO inhalation, and antibiotics should be instituted.

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