Bronchopulmonary dysplasia (BPD) remains one of the most common and severe diseases in very preterm infants, which can cause death. Since the first description of BPD in 1967, not only understanding of the disease’s nature, its definition, classification, epidemiology, features of the clinical course, diagnosis, prevention, treatment, and prognosis but the specific autopsy histopathological features have changed. The primarily reason for this is considered a change in the population of sick and dead infants as a result of improving clinical practice, increasing the survival rates of the most immature neonates, and reducing the incidence of severe BPD forms and the associated mortality.

The BPD form that has been described initially is now called "old" BPD and is characterized by significant lung injury. In the smallest neonates, who were treated with exogenous surfactant, the histopathological signs of the disease changed, determining the need to modify the theoretical concept of BPD. The leading feature of the new BPD form was the disorder of lung development and formation, not their injury. Morphologically, this was manifested by a reduced number and simplified structure of acini, changes in the capillary structure with less obvious fibrosis of the lungs. Such morphometric methods as the radial alveolar count and the count of mean number of alveoli intercepts can be used for the histopathological diagnosis of a simplified lung structure. The use of these techniques helps to objectively assess lung growth retardation. Although the number of cases of "new" BPD currently prevails, some autopsies are still characterized by histopathological changes typical for the "old" form of the disease. A combination of classic and new features is also possible. When establishing a pathological diagnosis of BPD, it is essential to consider all specific histopathological changes that may indicate the presence and severity of the disease, as well as its role in thanatogenesis. This is important not only for the correct postmortem diagnosis of BPD, but also for the studying of various disease phenotypes.

The article describes the main histopathological characteristic of various BPD forms, as well as methods of evaluating the simplified lung structure.

Keywords: bronchopulmonary dysplasia; histopathology; preterm infants.
stage, which lasts 2-3 days), the regeneration period (the 2nd stage, 4-10 days), the period of transformation into chronic lung disease (the 3rd stage, 10-20 days) and the period of chronic lung disease (stage 4, later one month) [9]. A few decades later, Cherukupalli et al. similarly described the histopathology of the period of acute lung injury (RDS), as well as the proliferative, early, and late recovery phases in 48 infants who died from RDS or BPD [10].

Numerous studies confirmed the described Northway et al. histopathological changes in the lungs of infants with BPD. However, most of them neither contained quantitative data nor analyzed the detected changes depending on the gestation age [4]. At the same time, as early as 1982, one of the publications described a critical decrease in the number of alveoli (10% of the norm) in a 33-month-old child who was born with a gestation age of 30 weeks and died of BPD [11].

As described by Northway et al. histopathological changes in the lungs of deceased infants are now called "old" BPD and are associated with lung injury caused by the harmful effects of endotracheal intubation, mechanical ventilation, and high oxygen concentrations. Death in such infants is mainly a consequence of severe respiratory failure in combination with a pulmonary heart [12].

The introduction of new methods of treatment and care of preterm infants, as well as more survival of the most immature babies, caused not only changes in the clinical course of the disease but also the morphological evolution of BPD. The infants described in the study by Northway et al. today die infrequently and survive mostly without chronic respiratory sequelae. Under the influence of the wider use of antenatal steroid prophylaxis, non-invasive respiratory support, and exogenous surfactant, as well as new safer methods of mechanical ventilation, the morphological signs of injury to immature lungs have changed. The change in the histological features of BPD in the post-surfactant era formed the concept of the "new" BPD [5]. Preterm birth during the canalicular and saccular stages of lung ontogenesis with the beginning of pulmonary gas exchange interrupts the normal development of the lungs, disrupting the processes of formation of alveoli and pulmonary vessels [13]. These changes are the main features of the "new" BPD, which can develop in extremely preterm babies who neither had severe RDS nor required mechanical ventilation after birth [5].

The histopathological features of the "new" BPD are mainly established on autopsies, biopsy data [14,15], as well as in experimental animal studies. Husain et al. [14] analyzed autopsy data from 22 BPD patients (14 surfactant-treated infants and 8 infants managed without surfactant administration), comparing them with data from 15 age-matched controls. The gestational age of most infants with BPD was less than 30 weeks. The authors described a smaller number of simplified alveoli, minor airway damage, a smaller number of dysmorphic capillaries in combination with less significant arterial changes, variable airway smooth muscle hyperplasia, and variable interstitial fibroproliferation. These changes were proposed as histopathological features of the "new" BPD. Alveolar septal fibrosis was significantly less and generally more diffuse in surfactant-treated infants. Instead, as a histopathological marker of new BPD, the authors proposed the presence of large alveoli with a small number of secondary septa in the distal acini of the lungs. In all lung samples obtained from patients with BPD at a postmenstrual age of more than 40 weeks the formation of alveoli was disturbed, which was confirmed by objective morphometric methods. The use of exogenous surfactant did not accelerate the formation of acini in the lungs of infants with BPD [14]. Simplification of distal lung acini and absence of alveolar septa were also the main changes in all lung biopsies studied by Coalson [15]. At the same time, the degree of cell infiltration and fibrosis in simplified alveolar structures was variable [15].

The main histopathological differences between "old" and "new" BPD were summarized by Coalson [15] and Hayes et al. [16] (Table 1).

In practice, several morphometric methods can be used to confirm a smaller number of alveoli in an infant's lungs. The method of radial counting of the number of alveoli (radial alveolar count, RAC) [17] determines the number of alveoli that are crossed by a perpendicular line drawn from the center of the respiratory bronchiole to the edge of the acinus (the nearest septal division or the edge of the pleura) (Fig. 2) [18]. This method provides determination of the reliable lung growth index during intrauterine, early and late postnatal development, as well as during childhood [19, 20]. It was established that counting in 40 fields of view is more accurate than counting in 10 fields [20]. However, regardless of the number of fields of view used, the same magnification must be applied and the average value calculated. Lung study using this method in a cohort of stillborn fetuses and dead newborn babies made it possible to determine the approximate normal number of alveoli for different age children groups (Table 2) [20].

Another morphometric method to assess the degree of lung alveolarization is the calculation of the average number of alveolar septa crossed by a standard ruler (mean linear intercept, MLI). This indicator, determining the size of the alveoli, also reflects the degree of the structure simplification, which is compensated by an increase in their size. It is determined by counting the number of alveolar septa that fall on a 1-mm ruler placed in the center of the field (Fig. 3). All fields of view should have the same...
magnification [21]. The following formula is used [14]:

\[ Lm = N \times L/m, \]

where Lm is the average number of alveolar septa crossed by a standard ruler, N is the number of fields of view, L is the length of the ruler (1 mm), and m is the number of alveolar septa.

Table 1

Evolution of the histopathological of BPD according to Coalson [15] in the modification of Hayes et al. [16]

<table>
<thead>
<tr>
<th>Old BPD</th>
<th>New BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alternating areas of atelectasis and emphysema</td>
<td>• Reduced, large and simplified alveoli (alveolar hypoplasia, reduced acinar complexity)</td>
</tr>
<tr>
<td>• Obvious airway epithelial lesions (hyperplasia and squamous cell metaplasia)</td>
<td>• Mild airway epithelium lesions</td>
</tr>
<tr>
<td>• Reduction of the internal surface area and alveoli</td>
<td>• Variable airway smooth muscles hyperplasia</td>
</tr>
<tr>
<td>• Airway smooth muscles hyperplasia</td>
<td>• Variable interstitial fibroproliferation</td>
</tr>
<tr>
<td>• Significant fibroproliferation</td>
<td>• Reduced number of dysmorphic capillaries</td>
</tr>
<tr>
<td>• Obvious vascular hypertensive changes</td>
<td>• Milder arterial/arteriolar vessels lesions</td>
</tr>
<tr>
<td>• Less alveolar septal fibrosis, but more diffuse</td>
<td>• Less arterial/arteriolar vessels lesions</td>
</tr>
</tbody>
</table>

Table 1

Estimated number of alveoli, determined by radial counting, in different age groups of fetuses and infants [20]

<table>
<thead>
<tr>
<th>Gestational age, weeks</th>
<th>The average number of alveoli in one field</th>
<th>Postnatal age, months</th>
<th>The average number of alveoli in one field</th>
<th>Gestational age, weeks</th>
<th>The average number of alveoli in one field</th>
<th>Postnatal age, months</th>
<th>The average number of alveoli in one field</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>1.5</td>
<td>1</td>
<td>6.7</td>
<td>32</td>
<td>3.4</td>
<td>80</td>
<td>11.1</td>
</tr>
<tr>
<td>19</td>
<td>1.6</td>
<td>2</td>
<td>7.4</td>
<td>33</td>
<td>3.6</td>
<td>90</td>
<td>11.2</td>
</tr>
<tr>
<td>20</td>
<td>1.7</td>
<td>3</td>
<td>7.8</td>
<td>34</td>
<td>3.8</td>
<td>100</td>
<td>11.3</td>
</tr>
<tr>
<td>21</td>
<td>1.8</td>
<td>4</td>
<td>8.1</td>
<td>35</td>
<td>4.0</td>
<td>110</td>
<td>11.4</td>
</tr>
<tr>
<td>22</td>
<td>1.9</td>
<td>5</td>
<td>8.3</td>
<td>36</td>
<td>4.3</td>
<td>120</td>
<td>11.5</td>
</tr>
<tr>
<td>23</td>
<td>2.0</td>
<td>6</td>
<td>8.5</td>
<td>37</td>
<td>4.5</td>
<td>130</td>
<td>11.6</td>
</tr>
<tr>
<td>24</td>
<td>2.1</td>
<td>8</td>
<td>8.8</td>
<td>38</td>
<td>4.8</td>
<td>140</td>
<td>11.7</td>
</tr>
<tr>
<td>25</td>
<td>2.3</td>
<td>10</td>
<td>9.0</td>
<td>39</td>
<td>5.1</td>
<td>150</td>
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</tr>
<tr>
<td>26</td>
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<td>20</td>
<td>9.7</td>
<td>40</td>
<td>5.4</td>
<td>160</td>
<td>11.8</td>
</tr>
<tr>
<td>27</td>
<td>2.5</td>
<td>30</td>
<td>10.1</td>
<td>41</td>
<td>5.7</td>
<td>170</td>
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<tr>
<td>28</td>
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<td>40</td>
<td>10.4</td>
<td>42</td>
<td>6.0</td>
<td>180</td>
<td>11.9</td>
</tr>
<tr>
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<td>2.8</td>
<td>50</td>
<td>10.6</td>
<td>43</td>
<td>6.4</td>
<td>190</td>
<td>12.0</td>
</tr>
<tr>
<td>30</td>
<td>3.0</td>
<td>60</td>
<td>10.8</td>
<td>44</td>
<td>6.75</td>
<td>200</td>
<td>12.0</td>
</tr>
<tr>
<td>31</td>
<td>3.2</td>
<td>70</td>
<td>11.0</td>
<td>44</td>
<td>6.75</td>
<td>200</td>
<td>12.0</td>
</tr>
</tbody>
</table>

The described morphometric methods should be used for the diagnosis of "new" BPD in cases without classic histopathological sign of this disease as alveolar septa fibrosis. If the infant's postmenstrual age exceeds 40 weeks, the ratio of the radial alveolar count (RAC) to the mean linear intercept (MLI) less than 30 is diagnostic for "new" BPD [14].

This disease phenotype is also characterized by reduced secondary alveolar septation, which is a sign of alveoli structure simplification (Fig. 4).

In addition to determining the RAC and MLI, it is important to assess the presence and spread of fibrosis in the lung tissue. Fibrosis in the lungs can be focal, if it is limited to several separate acini, or diffuse, if it is present in all parts of the lungs (Fig. 5). It is also necessary to assess the presence or absence of necrotizing bronchiolitis, which is caused by the harmful effects of high oxygen concentrations and gas pressure during mechanical ventilation [14].

The concept of "new" BPD is mainly based on the "arrest of growth" of the lungs, and not on their injury [5,22]. However, there are currently signs that BPD is changing again. The number of infants requiring tracheostomy and mechanical ventilation is increasing due to the increased survival of extremely preterm with extremely low birth weight babies with complex medical problems [7]. In particular, the frequency of BPD in children with gestational age 23 weeks is about 78%, among which 58% is severe form of the disease [23]. Therefore, early mortality and survival with severe BPD remain a clinical challenge [6,24]. Differences in injury and repair patterns probably result from multiple lung dysmaturity phenotypes that are caused by antenatal and postnatal risk factors, as well as genetic background [25]. Thus, lung damage, which leads to the occurrence of BPD, is not uniform, and is manifested by various changes in lung structure [26]. Therefore, during the histological examination, it is essential to consider morphological signs of both "old" and "new" BPD.

An important point is making the diagnosis of BPD, which remains controversial despite the established criteria, as they are not perfect [27,28]. Currently, the definition and classification of BPD of the US National Institutes of Health (2001) as modified by Walsh et al. are recommended for use (2003). Diagnosis according to this classification is made by the presence of at least 28 days of oxygen dependence after birth [29,30]. At the same time, some preterm babies with significant lung injury may die before reaching 28 days of life from severe respiratory failure caused by existing BPD. In such a situation, according to the current classification, there is formally no basis for making
a clinical diagnosis of BPD, which may be the reason for discrepancies between clinical and pathological diagnoses. The National Institute of Child Health and Human Development (2016) proposed changes and clarifications to the classification and definition of BPD [31]. One of the new recommendations is the possibility to make a clinical diagnosis of BPD before preterm infant has reached 28 days of postnatal age in the case of death after 14 days of life due to persistent parenchymal lung disease and severe respiratory failure in the absence of other causes (e.g., necrotizing enterocolitis, intraventricular hemorrhage, episode of sepsis, etc.). However, this classification is not valid and is at the stage of discussion and testing. At the same time, an accurate pathological diagnosis of BPD, which takes into account all possible histopathological signs of this disease, is an important element of confirming the clinical diagnosis, as well as making the diagnosis when typical morphological changes in the lungs are already present, but the clinical criteria of the disease have not reached yet. On the other hand, the presence of histopathological changes in the lungs of a deceased infant, characteristic of BPD, does not automatically mean that BPD is the cause of the death of such a baby. In order to make such a conclusion, it is necessary to be sure that the infant really died from respiratory failure due to typical lung injury, and not because the other reasons mentioned above.

Therefore, extremely premature infants who die today with "new" BPD show minimal fibrosis and injury of the respiratory tract against a background of striking reduction in the number of alveoli and impaired microvessel development. These histopathological findings demonstrate that processes which interrupt normal lung development rather than lung injury cause the "new" BPD. Accordingly, the correct description and assessment of histopathological changes in the lungs are important not only for the correct postmortem diagnosis of BPD, but also for the studying of various disease phenotypes.
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МОРОФОЛОГІЧНІ ЕВОЛЮЦІЯ І ДІАГНОСТИКА БРОНХОЛЕГЕНЕВОЇ ДИСПЛАЗІЇ У ЗНАЧНО НЕДОНОШЕНІХ НЕМОВЛЯТ

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Резюме

Бронхолегенева дисплазія (БЛД) залишається одним з найпоширеніших і найтяжчих захворювань у значно недонощених немовлят, яке може бути причиною їх смерті. Від першого опису БЛД у 1967 р. змінились не лише розуміння природи цього захворювання, його визначення, класифікація, епідеміологія, особливості клінічного перебігу, лікування та смертності, але і відтак у біології та біохімії. Сучасна класифікація захворювання включає у себе також різні форми синдрому, які можуть виникати внаслідок наслідків змін анатомії та функцій легень у відповідь на різні системні захворювання. Це визначає обґрунтування істотної характеристики цього захворювання.

Ключові слова: бронхолегенева дисплазія; гістопатологія; передчасно народжені немовлята.

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