Unique problems of pneumonia in obese children:  
a literature review

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ABSTRACT
Background: Obesity in children has its impact when the child experiences infectious conditions common in childhood, such as pneumonia. The increasing incidence of obesity in children in the last three decades forms the basis for compiling this review article. This review article aims to provide current insights about the impact of obesity on respiratory physiology, inflammatory conditions in pneumonia, and drug pharmacodynamics.

Methods: This literature review uses the latest literature relevant to matters affecting pneumonia management and clinical approach in children with obesity. This literature was obtained from various sources of other scientific literature.

Results: Obesity affects the respiratory physiology of children to collapse more easily, energy use becomes less efficient, children become tired, and hypoxemia occurs easily. Obesity also increases the degree and ease of inflammation in pneumonia and affects the pharmacodynamics of several drugs commonly used to manage pneumonia.

Conclusion: Management of pneumonia in children with obesity requires vigilance and more stringent monitoring and adjustment of drug doses.

Keywords: Children, Obesity, Pneumonia, Review Article.

INTRODUCTION
Obesity is a condition in which there is an accumulation of excessive amounts of fat that poses a risk of causing health problems. The increase in the incidence of obesity is per the nutritional transition theory, which states that increased consumption of ultra-processed foods and decreased physical activity are the effects of rapid economic development, urbanization, and globalization. Obesity prevalence in children globally has increased eight times. From 0.7% to 5.6% in girls and 0.9% to 7.8% in boys from 1975 – 2016, Indonesia is transitioning to this nutrition state. Overweight and obesity incidence in children increased 3x (5.1% to 15.6%) for children aged 6-12 years and 2x (7.1% to 14.1%) for adolescents aged 13-18 years from 1993-2014. This places Indonesia as the country with the highest obesity in children in Southeast Asia.

Obesity occurs due to an imbalance between the amount of energy consumed and used. Some of the factors that cause obesity include patterns of overfeeding children by parents, overeating behavior as a maladaptive coping mechanism due to psychosocial pressure, and the wide availability of sweetened drinks, snacks, and fast food at low prices and easily accessible. Technological developments cause children to spend more time with sedentary activities such as playing computer games, watching television, and doing activities on personal social media. The impact of obesity on children is not only limited to childhood but continues into adulthood. In general, obesity stimulates a chronic inflammatory state resulting in multiple organ damage. The well-known impacts include cardiovascular, endocrine, musculoskeletal, gastrointestinal, dermatology, and neurology.

Pneumonia is a disease that causes significant morbidity and mortality in Indonesian children. The incidence of pneumonia in Indonesia is 31.4 per 100,000, placing Indonesia in the world’s top five countries with the most pneumonia in children. Pneumonia is a significant cause of child death in Indonesia. This disease is the number one cause of death for 29 days – 11 months, with a proportion of 14.4%, and number two for the age group 12 – 59 months, with 9.4%. This review discusses obesity-related problems in children with pneumonia.

Impact of obesity on respiratory physiology
Obesity affects respiratory physiology in healthy children and adolescents through several mechanisms:

1. Mechanics of respiration
Excess adipose tissue in the thorax and abdomen causes increased intra-abdominal pressure against the diaphragm and increased adipose tissue pressure in the thoracic cavity. This excess causes the ability to expand the thorax to decrease, which in turn causes interference with lung compliance. These changes then cause a decrease in lung volume and capacity and give rise to a picture of restrictive lung disease in the form of a decrease in functional residual capacity (FRC) and expiratory reserve volume (ERV). The decrease in FRC and ERV values in obesity were approximately 75% and 47%, respectively, compared to normal BMI conditions.

2. Oxygenation
Obese children have impaired oxygenation due to increased cardiovascular resistance, decreased lung compliance, and increased work of breathing.

3. Ventilation
Obese children have decreased airway diameters and increased airway resistance, which lead to increased work of breathing and decreased ventilation.

4. Efﬂux
Obese children have decreased efﬂux due to decreased muscle mass and decreased efﬂusion from the lung.

5. Perfusion
Obese children have decreased perfusion due to decreased cardiac output and decreased blood ﬂow to the lungs.

6. Ventilation/Perfusion mismatch
Obese children have decreased ventilation/perfusion mismatch, which leads to decreased oxygenation and increased carbon dioxide levels.

7. Respiratory muscles
Obese children have decreased respiratory muscles, which leads to decreased respiratory function and decreased ability to breathe.

8. Respiratory compliance
Obese children have decreased respiratory compliance, which leads to decreased lung function and decreased ability to breathe.

9. Respiratory effort
Obese children have increased respiratory effort, which leads to increased work of breathing and decreased lung function.

10. Respiratory acidosis
Obese children have increased respiratory acidosis, which leads to decreased pH levels and decreased oxygenation.

11. Respiratory alkalosis
Obese children have decreased respiratory alkalosis, which leads to increased pH levels and decreased oxygenation.

12. Respiratory compensation
Obese children have increased respiratory compensation, which leads to increased pH levels and decreased oxygenation.

13. Respiratory failure
Obese children have decreased respiratory failure, which leads to decreased oxygenation and increased carbon dioxide levels.

14. Respiratory death
Obese children have decreased respiratory death, which leads to decreased oxygenation and increased carbon dioxide levels.
FRC and ERV causes three things.9 a. The closing capacity of the lung is the volume at which the bronchioles collapse. If the closing capacity of the lungs is lower than the FRC, there will be enough air to keep the airways open. When the FRC falls below the closing capacity, the airway closes before complete expiration, and shutting and atelectasis will occur. Furthermore, during tidal respiration in obese children, flow-restricted segments form prematurely, especially in the lower lung tissue. Therefore, the small airways of obese children will collapse more and more quickly than children with average weight.
b. There is an inverse relationship between FRC and airway resistance. The collapsed alveoli cannot provide sufficient radial traction to keep the small airways open. As a result, the airway narrows, which in turn causes an increase in airway resistance. An increase in airway resistance causes an increase in elastic recoil, so obese children require more energy to produce tidal volume breaths.
c. Ventilation becomes inhomogeneous, increasing ventilation-perfusion inhomogeneity and eventually leading to hypoxemia. Especially when the FRC is <65% of predicted or the ERV is below 0.6 L.

2. Inflammation
Adipose tissue macrophages produce pro-inflammatory substances and hormones (adipokines). When they reach the systemic circulation, it will affect the immune response, thereby inducing bronchial hyperreactivity and reducing lung airflow.10 Adipose tissue comprises mature adipocytes, preadipocytes, mesenchymal cells, and stromal cells. This tissue has a role as a circulating triacylglycerol (TAG) storage depot and inhibits the release of free fatty acids. In obesity, adipocytes become saturated with TAG, so TAG and free fatty acid levels in circulation increase. Increasing TAG and free fatty acids in circulation lead to the storage of lipids in areas other than adipose tissue, like the skeletal muscle, pancreatic islets, and the liver. Free fatty acids are ligands for Toll-like receptor-4, so an increase in circulating fatty acids also causes systemic inflammation. Another function of white adipose tissue is as an endocrine organ by producing adipocytokines, cytokines, acute phase reactants, prostaglandins, and others. Adipocytokines are adipocyte-derived hormones that are similar to cytokines. In obesity, the ability to produce pro-inflammatory cytokines such as leptin, resistin, and visfatin increases. There is also an increase in mediators that increase the immune response, such as IL-6, TNF alpha, acute phase reactants, CRP, serum amyloid A, and complement C3.11 Conversely, the ability to produce anti-inflammatory adiponectin decreases. The relationship between adipocytes and inflammation, both systemic and local in the lung, is mutually influencing. Adipocyte cells that experience hypertrophy in large numbers in obese children will cause relatively insufficient blood vessel perfusion resulting in tissue hypoxia and apoptotic cell death. The cellular debris left behind from apoptotic adipocytes induces chemokines, such as monocyte chemotactrant protein-1, which then recruits macrophages and T cells from the peripheral circulation. Macrophages will produce TNF-α, IL-6, and other cytokines, which are pro-inflammatory mediators. The production of these pro-inflammatory mediators is counterproductive because they inhibit predisposition maturation, even though mature adipocytes can buffer increased TAG entry. Two things happened as a consequence. First, the TAG in the blood remains high, which increases systemic inflammation. Second, mature adipocytes undergo hypertrophy, hypoxia, and apoptosis, creating a continuous vicious circle that keeps the inflammation going. Pro-inflammatory mediators produced in adipose tissue can eventually enter the circulation and cause chronic systemic inflammation. Chronic systemic inflammation can potentially enhance the pulmonary immune response to respiratory infections.12 Conversely, inflammation in the lung will make adipocytes respond by producing adipocytokines and other inflammatory mediators that certainly add to the chronic inflammatory conditions that have occurred.13 Increased lung inflammation will cause: 1) increased leukocyte recruitment; 2) pro-inflammatory cytokine production increases; 3) increased microvascular permeability; and 4) more airway obstruction.14 Increased AHR in obesity can occur due to two mechanisms. They are, first, related to breathing patterns. Obese children have a low FRC, fast breathing patterns, and decreased tidal volumes that affect airway smooth muscle contractility (ASM). Stretching during regular tidal breathing and deep inspiration modulate smooth muscle contractility. Breathing at a lower tidal volume causes less load on the ASM, shortening faster, and adaptation to length (mechanical plasticity) occurs more efficiently - the ASM adapts so that it begins to contract at a shorter size. Another potential mechanism is that low tidal volumes may not interfere with the actin–myosin cross-bridges resulting in a more rigid ASM. The longer and more pliable ASM maintains airway lumen patency in healthy subjects even during the methacholine challenge. A shorter ASM accompanied by decreased FRC tidal stretching in obesity can reduce actin–myosin cross-bridge disturbances, causing AHR. Interestingly, AHR may not be visible during spirometry because the procedure requires the child to breathe until the total lung capacity is like a normal FRC, thereby eliminating AHR. Eliminating AHR during spirometry procedures is why studies on AHR in obese children show conflicting results.9 The inflammatory response of obese children to viral infections is also different. Obesity is associated with chronic inflammation and impacts the body’s immunity. The mechanism by which the response of the respiratory
system to viral infection increases in obese children is as follows. Leptin, a hormone-like cytokine that is positively associated with body mass index (BMI), mediates the upregulation of suppressor of cytokine signaling (SOCS) proteins. The SOCS protein then plays a role in negative feedback regulation of Janus-activated kinase signals – signal transducer and activator of transcription (JAK-STAT) and induction of interferon (IFN) types 1 and 2 and pro-inflammatory cytokines. The result is suppression of the immune response in obese children. In addition, the respiratory cell membrane of obese children has undergone modifications in the form of increased cholesterol. Cholesterol is a critical structural component for the binding and endocytosis of respiratory viruses, so the high cholesterol in the cell membrane allows the entry of respiratory viruses more easily. Another explanation is airway restriction and the possibility of other comorbidities in obese children. Different patterns of growth and development of the respiratory system according to age stages affect the complexity of the relationship between obesity and respiratory physiology. First, the growth pattern of the respiratory tract until the end of school age is synaptic. Namely, the airways’ growth is slower than the growth of the lung parenchyma. The growth of the respiratory tract after this phase follows an isometric pattern; namely, the airways’ growth rate is the same as that of the parenchyma. The synaptic pattern will increase airway resistance, and the risk of airway obstruction is higher, especially in boys with narrower airway calibers than girls. Second, the physical and hormonal changes that occur during puberty. An increase in the size of the anteroposterior and vertical diameter of the chest cavity marks growth acceleration during puberty. This size increase allows for increased lung capacity and volume. Growth in muscle mass also mainly occurs in adolescent boys, so the forced vital capacity (FVC) and respiratory flow also increase. In conclusion, the effect of obesity on respiratory physiology mainly occurs in children experiencing a dyskinetic phase, namely up to preschool age. 

**Impact of Obesity on Pneumonia in Children**

Obesity is a risk factor and disease modifier for several respiratory conditions, such as asthma, obstructive sleep apnea syndrome (OSAS), and acute respiratory tract infection. Risk factors are things that increase the likelihood of a disease occurring, while disease modifiers are things that modify the outcome of a disease. Acute lower respiratory tract infection is a disease that often occurs in children, especially in the age group <5 years. An exciting study from Arias-Bravo (2020) found that obese children show higher co-infection with Respiratory Syncytial Virus (RSV) than normal children (71% obese vs. 37% average body weight, p 0.013). The length of stay of children due to acute lower respiratory tract infections aged <6 months with obesity was also longer (RR 1.68, CI 95% 1.01 – 2.71) with more extended oxygen use (RR 1.91; CI 95% 1.15 – 3.15). Bramley et al. also reported the same, i.e., children with community-acquired pneumonia and obesity had a higher likelihood of being treated in the ICU (aOR 2.1; CI95% 1.4 – 3.2) or using a ventilator (aOR 2.7; CI 95% 1.3 – 5.6). Concerning COVID-19, an exciting study by Murillo-Zamora et al. found obesity as a risk factor for a positive SARS CoV2 PCR result with an aOR of 2.05 (95% CI 1.11 – 3.79), along with other risk factors, i.e., household contacts with COVID-19 sufferers (aOR 2.27; 95% CI 1.68 – 3.08) and ages 13 – 15 years (aOR 2.08; 95% CI 1.46 – 2.96). In contrast, the COVID-19 pandemic increases the likelihood of obesity in children and adolescents with lockdown policies and online schools, thereby reducing physical activity and increasing children's exposure to snacks. Karlson et al. reported the impact of obesity on rats treated with influenza and S. pneumoniae infections and a summary of drug dose adjustment in several medicines commonly used in children with pneumonia:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose adjustment</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Carabapenem, cephalosporin, metronidazole, penicillin, vancomycin, Ciprofloxacin</td>
<td>No dose adjustment is necessary.</td>
<td>Up to maximum adult dose</td>
</tr>
<tr>
<td>- Clindamycin</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td>- Gentamycin</td>
<td>No dose adjustment or AdjBW (correction factor 0.45)</td>
<td></td>
</tr>
<tr>
<td>- Ibuprofen, Paracetamol</td>
<td>AdjBW (correction factor 0.35) up to adult max</td>
<td></td>
</tr>
<tr>
<td>- Corticosteroids (dexamethasone and prednisolone)</td>
<td>AdjBW (correction factor 0.4) up to adult max</td>
<td></td>
</tr>
<tr>
<td>- Methylprednisolone</td>
<td>No dose adjustment is necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ideal body weight</td>
<td></td>
</tr>
</tbody>
</table>
with non-lethal strains and doses. Obese rats showed higher mortality and a faster increase in viral and bacterial titers in the airways than experimental rats that were not obese. Interestingly, obese mice receiving influenza and pneumococcal vaccinations could not produce protective antibodies.22

Effects of obesity on drug pharmacokinetics in children

The Pharmacokinetics of drugs is a combination of body structure and function and drug-related properties. In obesity, there are changes in organ size, composition, function, and drug-related properties such as physicochemistry and absorption, distribution, metabolism, and elimination properties [ADME]. The effect of obesity on drugs is specific for each drug, so a universal dosing scheme for obesity is impossible.23 Kyler et al. reported that antibiotics and antipyretics were the most prescribed drugs for obese children, both inpatient and outpatient. Unfortunately, there has not been much research on whether or not a dose adjustment is necessary for children with obesity for most of these drugs.24

The Pediatric Pharmacy Advocacy Group recommends that, if there are no specific studies yet, then dosing the drug empirically in overweight/obese children according to the following guidelines:25-27
- Weight-based doses are used when body weight is <40kg and ≥40kg as long as fewer than the maximum adult dose.
- Need to know the maximum recommended adult dose.
- Clinicians should consider modifying PK parameters to adjust drug dosages in children with overweight/obesity.

We can use three body weight parameters to calculate drug doses for children with obesity. The first is total body weight, which is the actual body weight. The second is ideal body weight, the child’s weight at the 50th percentile according to the child’s actual height. The third is adjusted body weight, using the formula IBW + [correction factor x (TBW - IBW)]. Correction factor values vary between 0.35 - 0.45 based on research. If there is no data from the research, we can use a value of 0.35 as a pragmatic approach.26-30

The Neonatal and Pediatric Pharmacist Group (NPPG) recommends several drug dose adjustments for children with obesity, according to Table 1 above.

The limitation of this literature review is that there is still little literature on drug dosage adjustments in children with obesity. Most of the dosage adjustment recommendations are based on studies for adults. Special research regarding drug dosage adjustment in children with obesity needs to be done.

CONCLUSION

In conclusion, strategic management in pneumonia of children with obesity is more cautious about the deterioration, more closed monitoring, more aggressive oxygenation therapy, higher possibility of antibiotic escalation, and dosage adjustment of medicine used.

CONFLICT OF INTEREST

There was no conflict of interest in writing this literature review.

ETHICAL CONSIDERATION

This literature review has followed ethical guidelines in scientific publications based on the COPE and ICMJE protocols.

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AUTHOR’S CONTRIBUTION

The author fully contributes to the ideas and conceptual framework, collection, analysis and interpretation of data in the literature and contained in scientific narratives.

REFERENCES


