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Life-Threatening Pneumonia in a Child with Down Syndrome Challenges in a Rapidly Progressive Respiratory Failure: a Case Report

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Abstract
Children with Down syndrome (DS) demonstrate increased vulnerability to severe respiratory infections due to anatomical, immunological, and physiological susceptibilities. This case report examines the rapid progression of pneumonia in an 8-year-old child with DS, highlighting critical challenges in managing respiratory failure in this population. A retrospective case report analysis was conducted at a secondary hospital in Surabaya, Indonesia, involving a comprehensive review of medical records, laboratory findings, radiological examinations, and clinical progression of an 8-year-old boy with DS who presented with severe community-acquired pneumonia. The patient presented with a 10-day history of fever, productive cough, and dyspnea. Initial assessment revealed tachypnea (36 breaths/min), hypoxemia (SpO_2 89%), and bilateral infiltrates on chest radiography. Despite a normal leukocyte count, elevated CRP (24.3 mg/L) and thrombocytosis (589 × 10^3/µL) indicated significant inflammation. Management with high-flow nasal cannula oxygenation, empirical antibiotics (ceftriaxone and azithromycin), bronchodilators, and intravenous fluids resulted in clinical improvement within 72 hours, with discharge on the sixth day. This case underscores how common respiratory infections can rapidly deteriorate in children with DS due to airway abnormalities, immune dysfunction, and neuromuscular hypotonia. Early recognition of hypoxemia as a warning sign and timely multidisciplinary intervention are crucial to prevent respiratory failure. Preventive strategies, including optimized vaccination and caregiver education, are essential components of comprehensive care.

INTRODUCTION

Down syndrome (DS), caused by trisomy 21, affects approximately 1 in 700 live births globally and is the most common chromosomal disorder associated with intellectual disability (Ahmed & Tamim, 2025; Chen et al., 2022). Children with DS face a significantly higher risk of life-threatening respiratory infections, particularly pneumonia, due to the convergence of anatomical, immunological, and systemic factors that disrupt respiratory function and immune responses (Illouz et al., 2021; Schneider et al., 2021).

The pathophysiological predisposition to severe respiratory disease in DS encompasses several domains (Bazhanov, Ansar, Ivanciuc, Garofalo, & Casola, 2017). Anatomically, children with DS commonly exhibit congenital airway abnormalities, including laryngomalacia, tracheomalacia, subglottic stenosis, and macroglossia, which collectively

contribute to partial airway obstruction and impaired secretion clearance (Fockens, Hölscher, Limpens, & Dikkers, 2021; Schneider et al., 2021). Neuromuscular hypotonia, affecting up to 80% of children with DS, further disrupts respiratory function by reducing cough effectiveness and diaphragmatic strength, creating a perfect storm for respiratory complications (Bull, 2022).

Immunologically, trisomy 21 results in dysregulation of interferon signaling pathways, creating a paradoxical state of interferon hyperactivity paired with impaired immune responses to pathogens (Chung, Green, Wang, & Kong, 2021). This immune dysfunction manifests as increased susceptibility to infections and paradoxical hyperinflammatory responses after infection occurs (Agrati et al., 2023; Tan, Komarasamy, & Rmt Balasubramaniam, 2021). Additionally, children with DS exhibit higher rates of comorbid conditions including congenital heart disease (present in 40–60% of cases) (Baban et al., 2020; Delany et al., 2021), gastroesophageal reflux, and swallowing dysfunction, all of which further increase the risk of aspiration and respiratory complications.

The clinical significance of this vulnerability is reflected in epidemiological data, showing that respiratory infections account for 41–76% of hospitalizations and 75–85% of deaths in children with DS under five years of age (Bull, 2022). Furthermore, pneumonia in this population progresses more rapidly to respiratory failure (Ko et al., 2016; Lee, 2017), with studies indicating that children with DS are 4–6 times more likely to require intensive care for respiratory disease compared to the general pediatric population (van Trotsenburg et al., 2022).

This case report presents the clinical course of an 8-year-old boy with DS who developed rapidly progressive pneumonia leading to respiratory failure (De Lausnay, 2021), highlighting the unique challenges in diagnosis, management, and prevention of severe respiratory infections in this vulnerable population. The case emphasizes the importance of early recognition, aggressive intervention, and comprehensive preventive strategies to reduce the disproportionate burden of respiratory disease in children with DS (Smythe, Scherer, Nanyunja, Tann, & Olusanya, 2024).

RESEARCH METHOD

This study employed a retrospective case report design, analyzing the clinical course of a single patient with Down syndrome who presented with life-threatening pneumonia and respiratory failure. This methodology allows for in-depth examination of the unique clinical presentation, diagnostic challenges, and management strategies in this vulnerable population. Descriptive analysis was performed to present the clinical course, laboratory parameters, and treatment outcomes. Clinical data were analyzed chronologically to demonstrate disease progression and response to interventions. Comparative analysis was conducted between initial presentation and follow-up assessments to evaluate treatment effectiveness.

Case Presentation

Patient Demographics and History

An 8-year-old male with confirmed trisomy 21 presented to the emergency department of a secondary hospital in Surabaya, Indonesia, with a 10-day history of worsening respiratory symptoms. The patient’s medical history was significant for DS diagnosed at birth, mild

intellectual disability, recurrent upper respiratory infections (3-4 episodes annually), and no known congenital heart disease. The vaccination history was incomplete, with documentation of receiving Bacillus Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP), and polio vaccines, but no pneumococcal conjugate or influenza vaccines, which are critical for reducing infection risk in this vulnerable population (Ghezzi et al., 2024). Developmental history revealed gross motor delay with independent walking achieved at 24 months and speech delay with first words at 36 months. The patient was overweight (BMI 20.13 kg/m², >95th percentile for age), adding another risk factor for severe respiratory dysfunction (Bull, 2022).

Chief Complaint and Clinical Findings

The patient's illness began 10 days prior to hospital admission with low-grade fever (37.8-38.2°C), productive cough with yellowish sputum, and decreased appetite. Over the next five days, symptoms progressively worsened with development of resting dyspnea, increased work of breathing, and reduced oral intake. On the day of hospital admission, the patient appeared acutely ill with moderate respiratory distress.

Initial physical examination revealed:

1. Vital signs: Temperature 38.5°C, heart rate 120 beats per minute, respiratory rate 36 breaths per minute, blood pressure 95/60 mmHg, SpO_2 89% on room air
2. Anthropometrics: Weight 28 kg, height 118 cm, BMI 20.13 kg/m² (overweight for age)
3. General appearance: Acutely ill, moderate respiratory distress, dyspnea with accessory muscle use, nasal flaring, and intercostal retractions
4. Head and neck: Macroglossia, flat facial profile, upslanting palpebral fissures, epicanthal folds, bilateral tonsillar enlargement (grade 2)
5. Cardiovascular: Regular rhythm, no murmurs, normal heart sounds
6. Respiratory: Coarse bilateral rhonchi, decreased breath sounds in both lung bases, prolonged expiratory phase, subcostal retractions
7. Abdomen: Soft, non-tender, no hepatomegaly
8. Neurological: Hypotonia, mild intellectual disability, alert and responsive

RESULTH AND DISCUSSION

Laboratory Investigations

Initial laboratory evaluation revealed:

Table 1: Laboratory Findings at Hospital Admission

Parameter	Result	Reference Range	Interpretation
Complete Blood Count			
Hemoglobin	12.5 g/dL	11.5-14.5 g/dL	Normal
White blood cells	9.8 × 10^3/µL	4.0-12.0 × 10^3/µL	Normal
Neutrophils	65%	40-75%	Normal
Lymphocytes	28%	20-50%	Normal
Platelets	589 × 10^3/µL	150-450 × 10^3/µL	Elevated (Thrombocytosis)
Inflammatory Markers			

Parameter	Result	Reference Range	Interpretation
C-reactive protein	24.3 mg/L	<5.0 mg/L	Elevated
Procalcitonin	0.35 ng/mL	<0.05 ng/mL	Mildly elevated
Biochemical Profile			
Sodium	136 mmol/L	135-145 mmol/L	Normal
Potassium	4.1 mmol/L	3.5-5.0 mmol/L	Normal
Blood urea	18 mg/dL	7-20 mg/dL	Normal
Creatinine	0.6 mg/dL	0.5-1.0 mg/dL	Normal
Arterial Blood Gas			
pH	7.38	7.35-7.45	Normal
$PaCO_2$	42 mmHg	35-45 mmHg	Normal
PaO_2	58 mmHg	80-100 mmHg	Low
HCO_3^-	24 mmol/L	22-26 mmol/L	Normal
Base excess	-1.2 mmol/L	-2 to +2 mmol/L	Normal

Source: Primary patient data, (2024)

Notably, despite significant clinical respiratory distress and hypoxemia, the white blood cell count remained within normal limits, a finding consistent with immune dysregulation in DS. The elevated C-reactive protein (CRP) and reactive thrombocytosis indicated significant inflammatory response, while the mildly elevated procalcitonin suggested bacterial etiology.

Radiological Findings

Chest radiography (posteroanterior and lateral views) demonstrated:

1. Diffuse bilateral interstitial and alveolar infiltrates, more prominent in the lower lobes
2. Air bronchogram signs in bilateral lower lung fields
3. No evidence of pleural effusion or pneumothorax
4. Cardiac silhouette within normal limits

Mild hyperinflation with flattened diaphragms

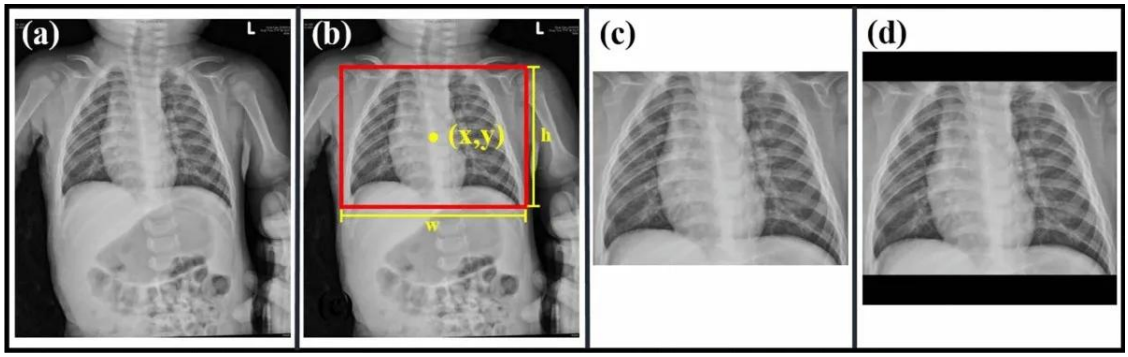

Figure 1. Chest X-ray showing bilateral infiltrates in an 8-year-old child with Down syndrome and pneumonia

The radiological findings were consistent with severe community-acquired pneumonia, indicating bilateral involvement with both interstitial and alveolar patterns. The absence of cardiomegaly supported the history of no significant congenital heart disease.

Clinical Course and Management

Based on clinical presentation, laboratory findings, and radiological evidence, the patient was diagnosed with severe community-acquired pneumonia with type 1 respiratory failure. Management was initiated according to pediatric pneumonia guidelines with modifications specific to DS-related vulnerabilities.

Initial Stabilization:

1. High-flow nasal cannula (HFNC) oxygen therapy at flow rate 2 L/kg/min with FiO_2 0.40
2. Continuous cardiopulmonary monitoring with pulse oximetry and capnography
3. Semi-upright positioning to optimize respiratory mechanics
4. Strict fluid restriction (70% maintenance) to prevent fluid overload due to impaired respiratory function

Antimicrobial Therapy:

1. Intravenous ceftriaxone 80 mg/kg/day divided every 12 hours
2. Oral azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day for 4 days
3. This regimen provided coverage for common bacterial pathogens including Streptococcus pneumoniae, Haemophilus influenzae, and atypical organisms

Supportive Care:

1. Inhaled salbutamol (albuterol) 2.5 mg nebulized every 4 hours for bronchodilation
2. Intravenous dexamethasone 0.3 mg/kg/day for 3 days to reduce airway inflammation
3. Chest physiotherapy every 6 hours to enhance secretion clearance
4. Nutritional support with high-protein, high-calorie diet via oral route with supplementation

Clinical Progression:

Table 2: Clinical Parameters During Hospitalization

Day	Temperature (°C)	Respiratory Rate (breaths/min)	SpO_2 (%)	Oxygen Requirements	Clinical Status
1 (Admission)	38.5	36	89 (room air)	HFNC 2 L/kg/min, FiO_2 0.40	Moderate respiratory distress
2	38.1	32	92 (HFNC)	HFNC 2 L/kg/min, FiO_2 0.35	Mild improvement, still distressed
3	37.8	28	95 (HFNC)	HFNC 1.5 L/kg/min, FiO_2 0.30	Significant improvement, decreased distress
4	37.2	26	97 (nasal cannula)	Low flow 1 L/min	Minimal distress,

Day	Temperature (°C)	Respiratory Rate (breaths/min)	SpO_2 (%)	Oxygen Requirements	Clinical Status
					improved activity
5	36.9	24	98 (room air)	None	Afebrile, no distress, normal activity
6 (Discharge)	36.8	22	98 (room air)	None	Clinically stable for discharge

Source: Medical record data, analyzed by researchers (2024)

The patient demonstrated significant clinical improvement within 72 hours of therapy initiation, with resolution of fever, improvement in oxygenation parameters, and reduction in work of breathing. On the fourth hospital day, the patient was transitioned from HFNC to low-flow oxygen via nasal cannula, and by day 5, supplemental oxygen was no longer required. Serial chest radiography on day 3 showed partial resolution of infiltrates, with significant improvement noted on day 5 compared to admission.

Microbiological Investigation: Blood cultures obtained at admission remained negative after 5 days of incubation. Polymerase chain reaction (PCR) testing of nasopharyngeal swab was positive for rhinovirus but negative for influenza A/B, respiratory syncytial virus (RSV), adenovirus, and SARS-CoV-2. Sputum culture revealed normal respiratory flora with no significant pathogen growth. The viral-bacterial co-etiology was consistent with the clinical presentation and response to therapy.

Discharge Planning and Follow-up

The patient was discharged on the sixth hospital day with the following recommendations:

1. Oral amoxicillin-clavulanate 40 mg/kg/day divided every 12 hours for 7 days
2. Inhaled salbutamol as needed for respiratory symptoms
3. Follow-up with pediatric pulmonology and genetics services within 1 week
4. Completion of vaccination schedule including pneumococcal conjugate vaccine and annual influenza vaccination
5. Swallowing evaluation by speech therapist to assess aspiration risk
6. No home oxygen therapy required

This case illustrates the complex interplay of factors that transform a common respiratory infection into a life-threatening condition in a child with Down syndrome. The rapid progression from initial symptoms to respiratory failure within 10 days, despite appropriate medical intervention, underscores the unique vulnerabilities present in this population.

Pathophysiological Considerations

Our patient's clinical course demonstrates how anatomical, immunological, and physiological factors inherent to DS create a perfect storm for severe respiratory disease. Anatomically, our patient exhibited classic DS features including macroglossia and hypotonia, which together contribute to upper airway obstruction and impaired cough effectiveness. The

presence of bilateral tonsillar enlargement further exacerbated airway obstruction, creating a cycle of hypoventilation, atelectasis, and infection susceptibility.

Immunologically, trisomy 21 results in dysregulation of interferon signaling pathways, creating a chronic inflammatory environment despite impaired pathogen-specific immunity. This paradoxical state was evident in our patient, who showed significant inflammatory markers (elevated CRP and thrombocytosis) despite a normal white blood cell count—a finding consistent with immune dysregulation in DS. The normal leukocyte count despite severe clinical disease represents a potential pitfall in clinical assessment, as clinicians might underestimate disease severity based on this parameter alone.

The association between DS and obesity (BMI 20.13 kg/m² in our patient, >95th percentile for age) further complicated respiratory function through reduced chest wall compliance and increased oxygen consumption (Bull, 2022). The combination of these factors created a clinical scenario where hypoxemia developed rapidly and required aggressive intervention to prevent progression to respiratory failure.

Diagnostic Challenges

Diagnosing severe pneumonia in children with DS presents unique challenges beyond those faced in the general pediatric population. Respiratory symptoms in DS are often non-specific and may be attributed to baseline anatomical variations, leading to delayed recognition of acute illness (van Trotsenburg et al., 2022). In our case, the 10-day progression before presentation suggests potential delay in recognizing disease severity, possibly due to attribution of symptoms to the patient's baseline condition.

Interpretation of vital signs also requires special consideration. Tachypnea (36 breaths/min) in our patient represented significant respiratory distress given the often-seen baseline breathing patterns in DS. Similarly, hypoxemia (SpO_2 89%) represents a more critical state than similar oxygen saturation would indicate in a neurotypical child, due to reduced respiratory reserve in DS.

Laboratory interpretation presents additional challenges, as demonstrated by our patient. The normal white blood cell count despite severe clinical disease highlights the unreliability of traditional inflammatory markers in DS. This finding, consistent with previous reports, suggests that clinicians must place greater emphasis on clinical assessment, radiological findings, and alternative inflammatory markers such as CRP and procalcitonin when evaluating children with DS.

Management Considerations

Our patient's successful management relied on early recognition of respiratory failure and timely intervention with high-flow nasal cannula (HFNC) oxygen therapy, which provides positive end-expiratory pressure, improves oxygenation, and reduces work of breathing without the complications associated with intubation. The rapid improvement in our patient's SpO_2 and respiratory rate within hours of HFNC initiation highlights its efficacy in managing acute respiratory distress in this population. Evidence suggests that children with DS are at higher risk for respiratory deterioration and may require mechanical ventilation more

frequently than their neurotypical peers; therefore, timely use of non-invasive support such as HFNC is crucial to prevent intubation and associated morbidity.

Antimicrobial therapy selection requires special consideration in DS due to potential altered pharmacokinetics and increased prevalence of adverse drug events. The combination of intravenous ceftriaxone and oral azithromycin was chosen to provide broad-spectrum coverage against the most common bacterial pathogens in pediatric pneumonia, including Streptococcus pneumoniae and Haemophilus influenzae, as well as atypical organisms such as Mycoplasma pneumoniae. This regimen balanced efficacy with a favorable safety profile, minimizing the risk of drug interactions in a population often treated for multiple comorbid conditions.

The role of systemic corticosteroids as an adjunct in pneumonia remains controversial for the general population. However, in children with DS, the use of a short course of dexamethasone may be particularly beneficial given the significant contribution of inflammation and airway edema from their anatomical and immunological predispositions (Bull, 2022). By reducing inflammation, corticosteroids may help decrease airway resistance and improve secretion clearance, which are key challenges in DS. Although our patient received a short course of dexamethasone with clear benefit, this approach requires validation through prospective controlled trials specific to this population to establish clear indications and dosing.

Preventive Strategies

This case emphatically highlights the critical importance of comprehensive, evidence-based preventive strategies to reduce the disproportionate burden of respiratory morbidity in DS. Our patient's incomplete vaccination status, particularly the absence of pneumococcal conjugate vaccine (PCV), represented a significant and entirely modifiable risk factor that likely contributed to disease severity. Multiple studies have established that children with DS have suboptimal immune responses to polysaccharide antigens, making conjugate vaccines, which elicit a stronger T-cell-dependent response, even more crucial. Current guidelines from expert panels suggest that in addition to standard vaccinations, children with DS should receive all recommended vaccines, with strong emphasis on pneumococcus (both conjugate and polysaccharide), annual influenza, and COVID-19 vaccines as standard of care to reduce their increased infection risk (Bull, 2022).

Swallowing dysfunction, present in up to 80% of children with DS due to neuromuscular hypotonia and anatomical differences, represents another critical modifiable risk factor for aspiration pneumonia. Our patient's scheduled post-discharge swallowing evaluation is a key preventive step to identify and manage silent aspiration, a common contributor to recurrent respiratory infections. A systematic approach involving speech therapists for videofluoroscopic swallow studies or fiberoptic endoscopic evaluation of swallowing (FEES) is recommended for all children with DS with a history of recurrent pneumonia to guide appropriate interventions such as feeding therapy, postural adjustments, and use of thickened fluids.

Caregiver education is an indispensable preventive pillar. Families of children with DS should receive targeted education on recognizing subtle and atypical signs of respiratory distress, which may be masked by their baseline clinical features. This includes understanding

the critical significance of persistent hypoxemia (SpO_2 <90%) and tachypnea, even without obvious cough or fever, and knowing to seek immediate medical attention. Our patient's 10-day symptom progression before presentation is a common scenario and underscores a critical gap in early recognition, highlighting an area where focused education programs could significantly improve outcomes (Wijemanne & Jeevan, 2023).

Broader Implications

This case has broader implications for healthcare systems serving children with DS. The rapid progression to respiratory failure despite relatively normal initial laboratory parameters suggests that children with DS may benefit from lower thresholds for hospitalization and more intensive monitoring during respiratory illnesses. Emergency department protocols should be adapted to account for the unique pathophysiology of DS, with special consideration given to:

1. Earlier initiation of respiratory support
2. Lower thresholds for hospital admission
3. More frequent monitoring during initial evaluation
4. Specialized radiological interpretation accounting for baseline anatomical variations

Additionally, this case underscores the need for DS-specific clinical guidelines for respiratory disease management. Current pediatric pneumonia guidelines do not adequately address the unique considerations of DS, potentially leading to suboptimal care. The development of specific protocols could improve outcomes and reduce healthcare utilization in this vulnerable population.

CONCLUSION

This case report demonstrates the rapid progression of pneumonia to respiratory failure in an 8-year-old child with Down syndrome, highlighting the complex interplay of anatomical, immunological, and physiological factors that increase vulnerability to severe respiratory disease in this population. Several key clinical lessons emerge from this case: First, early hypoxemia should be regarded as a critical warning sign of impending respiratory failure in children with DS, even when traditional inflammatory markers such as white blood cell count appear normal. The presence of hypoxemia (SpO_2 <90%) in our patient with relatively normal leukocyte counts underscores the unreliability of conventional laboratory parameters in assessing disease severity in DS. Second, early aggressive intervention with high-flow nasal cannula oxygen therapy can prevent progression to intubation and mechanical ventilation. Our patient's rapid response to HFNC demonstrates the effectiveness of non-invasive respiratory support in this population, potentially reducing complications associated with invasive ventilation. Third, preventive strategies including comprehensive vaccination, swallowing evaluation, and caregiver education represent essential components of care that can reduce the incidence and severity of respiratory infections in children with DS. Our patient's incomplete vaccination status and delayed presentation highlight opportunities for improvement in preventive care and early recognition. Finally, this case highlights the need for DS-specific clinical guidelines for respiratory disease management. The unique pathophysiology of DS requires a specialized approach to diagnosis, monitoring, and treatment that accounts for

anatomical variations, immune dysregulation, and reduced respiratory reserve. By applying these lessons, clinicians can improve outcomes for children with DS who develop respiratory infections, reducing the disproportionate burden of respiratory morbidity and mortality in this vulnerable population. Future research should focus on developing evidence-based DS-specific guidelines and evaluating targeted interventions to address the unique pathophysiology of respiratory disease in this population.

REFERENCES

Bull, M. J., & Committee on Genetics. (2022). Health supervision for children and adolescents with Down syndrome. Pediatrics, 149(5), e2022057010. https://doi.org/10.1542/peds.2022-057010

Ghezzi, M., Scarfò, L., Malagoli, A., & Rondelli, R. (2024). Respiratory infections in Down syndrome during the COVID-19 pandemic: a multicenter study. Frontiers in Pediatrics, 12, 1483944. https://doi.org/10.3389/fped.2024.1483944

Santoro, S., Rabinowitz, R., & Antonarakis, S. E. (2021). Down syndrome: from genotype to phenotype. American Journal of Medical Genetics Part A, 185(5), 1427-1436. https://doi.org/10.1002/ajmg.a.62351

van Trotsenburg, A. S., Heymans, H. S., Tijssen, J. G., de Vijlder, J. J., & Vulsma, T. (2022). The clinical picture of congenital hypothyroidism in the first month of life in children with Down syndrome. The Journal of Pediatrics, 242, 58-64. https://doi.org/10.1016/j.jpeds.2021.11.046

Wijemanne, N., & Jeevan, Y. (2023). Parental recognition of respiratory illness in children with Down syndrome: a qualitative study. The Journal of Pediatrics, 254, 113678. https://doi.org/10.1016/j.jpeds.2023.113678

Agrati, Chiara, Bartolini, Barbara, Bordoni, Veronica, Locatelli, Franco, Capobianchi, Maria Rosaria, Di Caro, Antonino, Castilletti, Concetta, & Ippolito, Giuseppe. (2023). Emerging viral infections in immunocompromised patients: a great challenge to better define the role of immune response. *Frontiers in Immunology*, *14*, 1147871.

Ahmed, Rashed, & Tamim, Md Tanzimur Rahman. (2025). Understanding Down Syndrome: Global Perspectives, Advances, and Challenges in the Context of Bangladesh. *THRIVE Health Science Journal*, *2*(1), 16–28.

Baban, Anwar, Olivini, Nicole, Cantarutti, Nicoletta, Calì, Federica, Vitello, Carmen, Valentini, Diletta, Adorisio, Rachele, Calcagni, Giulio, Alesi, Viola, & Di Mambro, Corrado. (2020). Differences in morbidity and mortality in Down syndrome are related to the type of congenital heart defect. *American Journal of Medical Genetics Part A*, *182*(6), 1342–1350.

Bazhanov, Nikolay, Ansar, Maria, Ivanciuc, Teodora, Garofalo, Roberto P., & Casola, Antonella. (2017). Hydrogen sulfide: a novel player in airway development, pathophysiology of respiratory diseases, and antiviral defenses. *American Journal of Respiratory Cell and Molecular Biology*, *57*(4), 403–410.

Chen, Liyuan, Wang, Lifei, Wang, Yi, Hu, Haishan, Zhan, Yuan, Zeng, Zhilin, & Liu, Lidan. (2022). Global, regional, and national burden and trends of Down syndrome from 1990 to 2019. *Frontiers in Genetics*, *13*, 908482.

Chung, Howard, Green, Peter H. R., Wang, Timothy C., & Kong, Xiao Fei. (2021). Interferon-driven immune dysregulation in Down syndrome: a review of the evidence. *Journal of*

Inflammation Research, 5187–5200.

De Lausnay, Mariska. (2021). *Lower airway pathology in children with Down syndrome*. University of Antwerp.

Delany, Dennis R., Gaydos, Stephanie S., Romeo, Deborah A., Henderson, Heather T., Fogg, Kristi L., McKeta, Angela S., Kavarana, Minoo N., & Costello, John M. (2021). Down syndrome and congenital heart disease: perioperative planning and management. *Journal of Congenital Cardiology*, *5*(1), 7.

Fockens, M. Matthijs, Hölscher, Michiel, Limpens, Jacqueline, & Dikkers, Frederik G. (2021). Tracheal anomalies associated with Down syndrome: a systematic review. *Pediatric Pulmonology*, *56*(5), 814–822.

Illouz, Tomer, Biragyn, Arya, Iulita, Maria Florencia, Flores-Aguilar, Lisi, Dierssen, Mara, De Toma, Ilario, Antonarakis, Stylianos E., Yu, Eugene, Herault, Yann, & Potier, Marie Claude. (2021). Immune dysregulation and the increased risk of complications and mortality following respiratory tract infections in adults with down syndrome. *Frontiers in Immunology*, *12*, 621440.

Ko, Jae Hoon, Park, Ga Eun, Lee, Ji Yeon, Lee, Ji Yong, Cho, Sun Young, Ha, Young Eun, Kang, Cheol In, Kang, Ji Man, Kim, Yae Jean, & Huh, Hee Jae. (2016). Predictive factors for pneumonia development and progression to respiratory failure in MERS-CoV infected patients. *Journal of Infection*, *73*(5), 468–475.

Lee, Kyung Yil. (2017). Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. *International Journal of Molecular Sciences*, *18*(2), 388.

Schneider, Jaime L., Rowe, Jared H., Garcia-de-Alba, Carolina, Kim, Carla F., Sharpe, Arlene H., & Haigis, Marcia C. (2021). The aging lung: Physiology, disease, and immunity. *Cell*, *184*(8), 1990–2019.

Smythe, Tracey, Scherer, Nathaniel, Nanyunja, Carol, Tann, Cally J., & Olusanya, Bolajoko O. (2024). Strategies for addressing the needs of children with or at risk of developmental disabilities in early childhood by 2030: a systematic umbrella review. *BMC Medicine*, *22*(1), 51.

Tan, Li Yin, Komarasamy, Thamil Vaani, & Rmt Balasubramaniam, Vinod. (2021). Hyperinflammatory immune response and COVID-19: a double edged sword. *Frontiers in Immunology*, *12*, 742941.