



Review

# Necrotizing Pneumonia in Children: Early Recognition and Management

Yuanyuan Chen <sup>1,2</sup>, Lanxin Li <sup>1,2</sup>, Chenlu Wang <sup>1,2</sup>, Yuanyuan Zhang <sup>1,2,\*</sup> and Yunlian Zhou <sup>1,2,\*</sup>

<sup>1</sup> Department of Pulmonology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

<sup>2</sup> National Clinical Research Center for Child Health, Hangzhou 310052, China

\* Correspondence: chzyy@zju.edu.cn (Y.Z.); zhouyunlian@zju.edu.cn (Y.Z.)

**Abstract:** Necrotizing pneumonia (NP) is an uncommon complicated pneumonia with an increasing incidence. Early recognition and timely management can bring excellent outcomes. The diagnosis of NP depends on chest computed tomography, which has radiation damage and may miss the optimal treatment time. The present review aimed to elaborate on the reported predictors for NP. The possible pathogenesis of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae* and coinfection, clinical manifestations and management were also discussed. Although there is still a long way for these predictors to be used in clinical, it is necessary to investigate early predictors for NP in children.

**Keywords:** necrotizing pneumonia; prediction; treatment



**Citation:** Chen, Y.; Li, L.; Wang, C.; Zhang, Y.; Zhou, Y. Necrotizing Pneumonia in Children: Early Recognition and Management. *J. Clin. Med.* **2023**, *12*, 2256. <https://doi.org/10.3390/jcm12062256>

Academic Editor: Ralph Epaud

Received: 31 January 2023

Revised: 27 February 2023

Accepted: 2 March 2023

Published: 14 March 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Necrotizing pneumonia (NP) is a rare complication of community-acquired pneumonia (CAP) and is characterized by catastrophic illness and a prolonged hospital stay and disease course [1]. It has been reported that 3% of cases of CAP in the UK have complications. Although NP alone and those co-existing with one or more other forms of complications of CAP (including parapneumonic effusion, empyema, lung abscess and local complications) are still deemed to be rare, the incidence of pediatric NP has increased [2]. A French study found that the proportion of NP among hospitalized CAP was 4.5% from 2006 to 2009, and the rate doubled to 9% from 2009 to 2011 [3]. In the United States, a retrospective observational study including 80 cases of NP identified no cases in the period 1990–1993, 12 in the period 1993–1996 and 40 in the period 2001–2004 [4].

NP usually progresses rapidly in previously healthy children despite appropriate management. A study in Taiwan found that no underlying diseases may predict the occurrence of necrosis and/or abscess independently [5]. However, a recent study has shown that NP tended to occur in children with a complex chronic condition, and the mortality rate was higher than that of NP in previously healthy children [6]. NP is characterized by necrosis and liquification of lung parenchyma and loss of the normal pulmonary parenchymal architecture [7]. Moreover, NP is associated with a higher risk of complications such as parapneumonic effusion, pleural empyema, pyothorax, pneumothorax, pyopneumothorax, septic shock, respiratory failure, hemolytic uremic syndrome (HUS) and bronchopleural fistula (BPF) [8,9]. In view of the severity of NP and heavy burden of hospitalization especially in developing countries, early prediction and management are essential for good recovery and prognosis.

## 2. Etiology and Pathogenesis

*Streptococcus pneumoniae*, *Staphylococcus aureus* and *Mycoplasma pneumoniae* are the most common pathogens reported in children with NP. Other bacterial infections associated with NP in children include *Pseudomonas aeruginosa*, *Streptococcus mitis* spp., *Streptococcus pyogenes*,

*Klebsiella pneumoniae*, *Pseudomonas* spp., *Fusobacterium* spp., *Staphylococcus epidermidis*, *Enterobacter aerogenes*, *Burkholderia pickettii* biovar, *Mycobacterium tuberculosis*, and *Chromobacterium violaceum* [10–12]. Some viruses and fungi like influenza, parainfluenza, adenovirus, respiratory syncytial virus, Herpes group (including Cytomegalovirus, Varicella-Zoster and the Epstein–Barr Virus), *Aspergillus* spp., *Candida* spp., *Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces* spp. and *Cryptococcus neoformans* can also cause NP [6,10]. And a synergy between viruses and bacteria is common and sometimes lethal. In order to recognize earlier and develop novel therapeutic strategies, it is essential to understand the pathogenesis of NP.

### 2.1. *Streptococcus pneumoniae* (*Pneumococcus*)

*Pneumococcus* is a Gram-positive bacterium and is a leading cause of bacterial pneumonia in children worldwide. In 2000, it was reported that 741,000 children less than 5 years old (accounting for 36% of all-cause pneumonia deaths) succumb to pneumococcal pneumonia, with the majority of them from developing countries [13]. Necrotizing pneumococcal pneumonia in children was first reported in 1994 [14], and an increase in its prevalence has been observed since then. However, the detailed mechanism is still unknown.

The capsule polysaccharide is the major virulence factor. It assists pneumococcus in interacting with the epithelium, avoiding entrapment by nasal mucus and inhibiting opsonophagocytosis during infections [15,16]. According to structurally and antigenically different capsular polysaccharides, more than 100 serotypes have been identified until now. Pneumococcal conjugated vaccines (PCVs) bind the capsular polysaccharides to a carrier protein. It can promote the immune system of young children to produce an adequate response by enhancing immunogenicity [17]. In 2000, the 7-valent pneumococcal conjugated vaccine (PCV-7) protecting against seven serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) was first licensed in the United States [18]. Beginning in 2010, PCV-10 containing additional serotypes 1, 5, 7F and PCV-13 containing additional serotypes 1, 5, 7F, 3, 6A and 19A have become available for use [19]. The introduction of PCV-7 led to significant decreases in pneumonia in childhood but increased the incidence of NP caused by non-vaccine serotypes [20]. PCV-13 has been reported to reduce the incidence and hospitalization rates for empyema and parapneumonic effusion substantially without serotype shift [21,22]. Similarly, PCV-13 implementation decreased the hospitalization rate for NP in Italy significantly. However, the hospitalization rate increased during the late post-PCV-13 period, and serotype 3 was prevalent in both the pre- and post-PCV-13 periods, which confirmed the modest efficacy of PCV-13 against serotype 3 [23]. Serotypes 3 and 19A are associated with most necrotizing pneumococcal pneumonia [2] (Table 1).

**Table 1.** Prevalent serotypes of *Streptococcus pneumoniae* in NP.

Year	Country	No.	PCV Use in National Immunity Program	Prevalent Serotypes Pre-PCV	Prevalent Serotypes Post-PCV	PCV Coverage	References
1997–2006	Utah	33	PCV-7: 2001, 2 + 1	Pre-PCV7: 6B (40.0%), 19F (20.0%), 1 (20.0%) and 6A (20.0%)	Post-PCV7: 4 (3.6%), 1 (7.1%), 3 (39.3%), 7 (3.6%), 8 (3.6%), 17 (3.6%), 19 (14.3%) and 19A (14.3%)	PCV-7: 80%	[20]
2005–2019	Italy	43	PCV-13: 2010, 2 + 1	Pre-PCV13: 1 (18.2%), 3 (27.3%), 5 (9.1%), 7F (9.1%) and 19A (9.1%)	Early post-PCV13: 1 (25.0%), 5 (12.5%) and 7F (12.5%) Late post-PCV13: 3 (80.0%) and 12 (20.0%)	PCV-7: 62.8% PCV-13: 23.3%	[23]
2012–2016	Catalonia, Spain	35	PCV-13: 2016, 2 + 1	Not mentioned	Post-PCV13: 1 (14.3%), 3 (48.6%), 6B (2.9%), 7F (2.9%), 14 (5.7%), 19A (8.6%), 7A (5.7%), 6A/C (2.9%) and 12F/A/44/46 (2.9%)	PCV-13: 14.3%	[24]

In addition to the polysaccharide capsule, pneumolysin is another virulence factor that can breach the membrane barrier of cells as a pore-forming toxin. In vitro, respiratory epithelial cells can sense the osmotic stress of pore formation and then activate the p38 mitogen-activated-protein kinase [25]. The activation of mitogen-activated-protein kinase may lead to an increase in chemokines and neutrophil influx [26]. Pneumolysin may also activate complement and inhibit neutrophil respiratory burst and release of the antibacterial, vasodilatory and nitric oxide from macrophages [27]. In the later phases of lung infection, pneumolysin is released from the cytoplasm to the surrounding tissue by the lysis of pneumococcus caused by neutrophils or activation of Lyt A [28]. Then this may lead to widespread damage to host tissue and help pneumococcus survive. Nevertheless, the increased virulence contributed by pneumolysin is not universal. For example, serotype 1 ST306, which is associated with invasive pneumococcal diseases, produces nonhemolytic pneumolysin [29].

Pathologic examinations have shown that suppurative necrosis with extensive infiltration and accumulation of neutrophils in the lung parenchyma and coagulative necrosis with anucleated and eosinophilic cell contours in preserved outlines of lung architecture is observed in children with NP [30]. Therefore, cytokines that promote neutrophilic inflammation and activate coagulation may be associated with the severity of NP. For example, IL-8 can effectively recruit and activate neutrophils, and the level of IL-8 has been reported to be related to the severity of lung necrosis [31].

## 2.2. *Staphylococcus aureus*

*Staphylococcus aureus* is a Gram-positive, coagulase-positive bacterium. *Staphylococcus aureus* infections have increased in recent years and are mainly associated with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). The morbidity of CA-MRSA doubled in the past decade [32]. CA-MRSA has a higher proportion of *Staphylococcus aureus* producing Pantone-Valentine leucocidin (PVL) at 74–100%, which depends on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in each region [33]. And there is no significant difference in PVL concentrations between PVL-positive methicillin-sensitive *Staphylococcus aureus* (MSSA) and PVL-positive MRSA [34]. PVL-positive strains are often associated with rapidly progressive, hemorrhagic NP [35].

PVL is a pore-forming toxin consisting of two components, LukS-PV and LukF-PV. It can form pores in the cell membrane of phagocytic leukocytes, especially polymorphonuclear leukocytes (PMNs), leading to leukocyte destruction and tissue necrosis [36]. Recombinant PVL is commonly used in experiments to explore the effects of PVL. In vitro, PVL was found to be a strong inducer for the release of histamine, proinflammatory mediators (IL-8, leukotriene-B4), granule enzymes ( $\beta$ -glucuronidase, hydrolase and lysozyme) and the production of reactive oxygen metabolites as a consequence of its effects in the activation and lysis of PMNs [36,37]. The increased influx of PMNs, infiltration of inflammatory cells, local vasodilation and tissue injury may result from this action. Similarly, PVL has been shown to induce the release of IL-8 in a rabbit model of NP [38]. Recombinant PVL can trigger the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation inducing macrophage death and IL-1 $\beta$  secretion [39]. Recombinant LukS-PV alone has been shown to induce the release of inflammatory cytokines from alveolar macrophages, and the toxicity of recombinant LukS-PV and LukF-PV has been found to form pores on the membrane of alveolar macrophages through binding to C5a receptor [40].

$\alpha$ -hemolysin is another critical virulence factor associated with NP. Purified  $\alpha$ -hemolysin can establish a ferret NP model [41]. Like PVL,  $\alpha$ -hemolysin can also activate NLRP3 inflammasome to induce IL-1 $\beta$  production and programmed necrotic cell death [42].  $\alpha$ -hemolysin can induce platelet-neutrophil aggregates formation, which plays an important role in alveolar capillary destruction in hemorrhagic/necrotizing pneumonia caused by CA-MRSA [43]. In fact, NP may be a shared consequence of numerous virulence factors like PVL,  $\alpha$ -hemolysin, LukAB, Spa, toxic shock syndrome toxin-1, staphylococcal entero-

toxin B and C, collagen adhesion, alpha toxin, staphylococcal enterotoxin-like toxin X, microbial surface components recognizing adhesive matrix molecules, clumping factors A and B, SdrE and the PSMs [44–48]. PVL promotes increased production of proinflammatory factor Spa, and they work together to cause overwhelming inflammation and tissue necrosis [48]. Clumping factors A and B, SdrE and Spa are able to activate platelet aggregation [49]. PVL also upregulates the expression of microbial surface components recognizing adhesive matrix molecules, which may enhance tissue adherence and colonization of PVL-positive stains [48]. Toxic shock syndrome toxin-1, staphylococcal enterotoxin B and C and staphylococcal enterotoxin-like toxin X are superantigens that have the ability to stimulate dysregulated T-cell proliferation [46]. *Staphylococcus aureus* can survive and proliferate within human cells free from the host immune system and antibiotic treatment [50]. Intracellular *Staphylococcus aureus* may cause apoptotic and/or necrotic cell death with several virulence factors involved by disturbing the host cell  $\text{Ca}^{2+}$  homeostasis and inducing cytoplasmic  $\text{Ca}^{2+}$  overload [51]. One possible mechanism is to create receptor-independent pore formation from the inner side of the plasma membrane [51]. For instance,  $\alpha$ -hemolysin may induce  $\text{Ca}^{2+}$  permissive pores by nonspecifically integrating into membranes at high concentrations [52,53].

### 2.3. *Mycoplasma pneumoniae*

*Mycoplasma pneumoniae* is a common pathogen causing CAP in children and young adolescents. In some countries with PCV-13 included in national immunization programs, *Mycoplasma pneumoniae* has taken the leading role in pediatric CAP [54,55]. *Mycoplasma pneumoniae* is known as an “atypical” pathogen. In general, the clinical course of *Mycoplasma pneumoniae* pneumonia (MPP) is benign with high- or middle-grade fever and dry cough partly accompanied by chills, headaches and chest pain or tightness. In the past few years, there have been many reports of *Mycoplasma pneumoniae* NP in China and around the world [56,57]. One possible reason is that severe *Mycoplasma pneumoniae* pneumonia (SMPP) and refractory *Mycoplasma pneumoniae* pneumonia (RMPP) have been increasingly reported [58,59]. The appearance of macrolide resistance may have no effect on the disease severity, but delayed effective antimicrobial treatment can contribute to RMPP development and progress by leading to incapability to clear bacteria and excessive immune response [60,61]. In addition to the persistent infection, the older age of children with *Mycoplasma pneumoniae* NP may be associated with a strong immune response which is closely related to the severity of MPP [57]. Finally, severe bacterial or viral infections may follow or coincide with *Mycoplasma pneumoniae*, and NP may be the result of mixed infections [62,63]. Moreover, the early use of antibiotics makes the detection of coinfection with other pathogens more difficult.

Community-acquired respiratory distress syndrome (CARDS) toxin, membrane lipoproteins, hydrogen peroxide and superoxide are the main virulence factors of *Mycoplasma pneumoniae* [64]. CARDS toxin, the only exotoxin produced by *Mycoplasma pneumoniae*, possesses ADP-ribosyltransferase and cellular vacuolization properties [65]. ADP-ribosylation can induce inflammatory responses like activating NLRP3 inflammasome [66]. Thus CARDS toxin can cause cell swelling, nuclear lysis, cell vacuolization and ultimate cell death. Membrane lipoproteins, as lipopolysaccharides, can activate NLRP3 inflammasome and autophagy via TLR-4 [67]. Hydrogen peroxide and superoxide are both strong oxidants generated by *Mycoplasma pneumoniae* [68]. Moreover, superoxide has been reported to inhibit catalase activity [69]. Protein degradation and DNA lesions caused by hydroxylation and cell membrane damage caused by peroxidation of lipids may lead to cell death [70].

### 2.4. Co-Infection

Co-infection has the tendency to lead to severer pneumonia. In recent years, severe pediatric CAP caused by bacterial (pneumococcus, *Staphylococcus aureus*, *Pseudomonas aeruginosa*) or viral (adenovirus, rhinovirus, respiratory syncytial virus, parainfluenza virus, coronavirus, influenza virus, enterovirus, among others, respectively) coinfection

with *Mycoplasma pneumoniae* has been increasingly reported [71–73]. NP associated with influenza virus or parainfluenza virus infections prior to pneumococcus or *Staphylococcus aureus* infections has been long reported [47,74–78]. Children co-infected with influenza A and *Staphylococcus aureus* are more likely to cause severe complications rapidly and have a higher mortality rate partly because of the difficulty of getting accurate and timely treatment [76].

Several hypothetical mechanisms of influenza virus during co-infection have been reported. Influenza virus can increase bacterial adhesion and growth by damaging lung epithelial cells, upregulating the host cell surface receptors and removing terminal sialic acid residues from host glycoconjugates [79,80]. Dysregulation of the immune system induced by the influenza virus may hinder the ability to clear the bacteria, for example, impairing the innate and adaptive immune responses by suppressing the Th1 immune cascade and the production of CD4- and B- lymphocytes and upregulating the production of T regulator cells [80,81]. The effect of PVL to damage the airway epithelium by killing neutrophils and the release of neutrophil proteases may be promoted by the influenza virus, which activates the lung epithelium to induce a massive influx of neutrophils. This activation of epithelium leads to the development of NP [82]. The influenza virus has been shown to modulate host metabolism, which is closely related to the levels of inflammatory cytokines expression and the promotion of influenza virus replication [83,84].

### 3. Clinical Manifestations

The common clinical manifestations of NP have no difference from those of uncomplicated pneumonia, including fever, cough, sometimes with chest pain, emesis, abdominal pain, dyspnea, anemia and fatigue [2]. But patients with NP have a more serious clinical course, longer duration of fever and length of stay, higher mortality, higher incidence of extra-pulmonary complications such as septic shock, respiratory failure and HUS and pulmonary complications such as parapneumonic effusion, pleural empyema, pyothorax, pneumothorax, pyopneumothorax and BPF [8,85]. PVL-positive *Staphylococcus aureus* is associated with high fever and an enhanced risk of purulent expectoration and hemoptysis [10]. And it has been shown that erythroderma, leucopenia and airway bleeding can predict the mortality of PVL-positive Staphylococcal NP [86]. Age and gender have no significant influence on the incidence of NP. The majority of reported cases are previously healthy and immunocompetent children [85]. When patients have flu-like symptoms, we should consider the possibility of viruses, especially during influenza season. When patients have malnutrition, cardiopulmonary diseases, underlying immunodeficiency conditions, or an experience of traveling or being in contact with birds or other animals, we should take the possibility of fungi into account [87]. Influenza-MRSA coinfection usually happens in previously healthy adolescents. They may have leukopenia or neutropenia and need ECMO support [88].

The laboratory characteristics of NP are mainly associated with mild-to-moderate anemia, hypoalbuminemia and elevated inflammatory markers, like white blood cell (WBC) counts and C-reactive protein (CRP) levels [2]. The typical pleural fluid of NP caused by bacteria has increased WBC counts, high protein content, low glucose concentration and high lactate dehydrogenase (LDH) concentration, while *Mycoplasma pneumoniae* NP is often dominated by lymphocytes, high protein content and normal glucose concentration in pleural fluid [4,89]. And organisms may be seen on Gram- or acid-fast-stained smears. The results of radiologic examinations could be large cavities and pleural effusions in the X-ray or on chest computed tomography (CT) [10].

### 4. Prediction and Early Recognition

In spite of the serious condition of NP, it always has a good prognosis with early recognition and management. Due to the variable evolution of NP, physicians' awareness and experience, improved diagnostics, as well as the propensity of pathogens, is essential to predict the severity of the clinical course of CAP before deterioration happens.

#### 4.1. Chest Computed Tomography and Lung Ultrasound

Diagnostic imaging is indispensable to NP. Chest radiography can reveal the presence of large cavities and large pleural effusions, but its accuracy does not compare with that of chest CT, especially in the initial phase of NP [90]. Ultrasonography is an effective modality to detect parenchymal lesions, pleural thickening and pleural effusion with no radiation exposure, low cost and wide availability [91]. And it has been shown to be as effective as CT in the diagnosis of NP and has been proposed to be used in the follow-up of imaging [92]. More importantly, impaired perfusion of Doppler ultrasound can predict massive necrotic changes early [93]. In the future, the use of chest CT in children with NP may be limited to particular occasions when patients do not respond well to appropriate management or are suspected of having complications or even other diseases. Currently, contrast-enhanced chest CT is still the most sensitive modality for the diagnosis of NP and can differentiate NP from a lung abscess [94]. It has been observed through CT scans that liquefaction transits to cavitation within 48 h [4]. In the lung consolidation area of NP, there are multiple thin-walled cavities or vesicles which can fuse into a large cavity. Compared with a single thick wall cavity of lung abscess, NP has no enhancement at the edge of the cavity. Some cavities have liquid levels and gas surfaces [94]. Pulmonary consolidations present several weeks before cavities appear. It has been shown that the CT value of pulmonary lesions in NP was lower than that in non-NP and may help predict NP early [95]. In order to reduce radiation damage, recent studies tried to adopt a machine-learning radiomics model based on radiographic features observed on non-enhanced CT scans or low-dose CT scans to recognize pulmonary consolidation in the early stage of NP in children [96,97]. Moreover, studies have found that lower kV combined with high Iterative Reconstruction in the CT pulmonary angiogram can maintain image quality [98,99].

#### 4.2. Laboratory Data

The level of serum albumin has been extensively used to reflect the severity of patients' conditions [100], and a recent study found hypoalbuminemia on admission was common in the pediatric intensive care unit and is a good predictor of mortality [101]. So it is meaningful to measure serum albumin routinely for NP patients. A retrospective observational study has shown that serum albumin less than 30.8 g/L is an independent risk factor for massive necrosis compared with mild and moderate necrosis [85]. WBC counts and CRP levels are common inflammatory markers. Increased WBC ( $\geq 15.1 \times 10^9/L$ ) and CRP ( $\geq 121.5$  mg/L) may have predictive significance for NP in children [102]. LDH, a pan-necrosis marker, can be released by cells undergoing either primary or secondary necrosis [103]. The level of pleural fluid LDH is often  $>1000$  U/L in NP among children, while serum LDH is  $\geq 353.5$  U/L [2]. Thus, paying attention to the high level of LDH may be useful in informing clinicians of the possibility of ongoing necrosis or liquefaction of the pulmonary parenchyma [104]. In addition to these biomarkers that only predict the possibility of NP, some available biomarkers are expected to differentiate certain etiologies.

*Streptococcus pneumoniae* can produce neuraminidase which removes N-acetyl-neuraminic acid from cell membrane surfaces and exposes Thomsen-Friedenreich antigen (TA) present on erythrocytes, platelets and glomeruli [105]. The interaction between TA and anti-TA antibodies, called TA activation, can be assessed and might indicate a higher risk for NP [106]. Fetuin-A is a kind of sialoglycoprotein, and it can protect erythrocytes from TA exposure. The level of fetuin-A less than 340 mg/L might be a predictor for pneumococcal NP with or without HUS in children [107]. The presence of immature PMNs in peripheral blood, high CRP levels ( $>12$  mg/dL) and no underlying disease at presentation have also been identified as independent predictors of the occurrence of necrosis or/and abscess caused by *Streptococcus pneumoniae* [5].

The critical factor of the severity of staphylococcal NP is PVL but not methicillin resistance [108]. Current approaches for detecting PVL, including enzyme-linked immunosorbent assay [34], latex agglutination [109] and polymerase chain reaction [110] are costly and time-consuming and are not routinely used at most diagnostic laboratories. Thus,

it is promising to develop a rapid and affordable method for PVL detection, for instance, a novel lateral flow assay [111,112] and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry detecting PVL within minutes [113]. And metabolomics may be a good way to predict illness severity prior to clinical diagnosis. For example, a study found the concentrations of acetone, acetoacetate, fumarate and glucose have been shown to be more than 25-fold higher in the patient with methicillin-resistant *Staphylococcus aureus* pneumonia than those of patients with influenza pneumonia and healthy controls [114]. But the overall concentration of the urine samples can be influenced greatly by the hydration state of the patient, so further investigations are needed.

D-dimer is a biomarker of fibrin formation and degradation and has been extensively used to diagnose venous thromboembolism [115]. Recently D-dimer levels have also been used to assess the severity of MPP [116], and D-dimer > 1367.5 ng/mL has been recognized as the risk factor for NP caused by *Mycoplasma pneumoniae* in children. And the use of low molecular-weight heparin has been shown to reduce the risk of pulmonary necrosis [117]. Children with *Mycoplasma pneumoniae* pneumonia (MPP) infection are related to higher risks of blood coagulation and thrombosis. Several studies have shown that pulmonary embolism, stroke, splenic infarction, myocardial infarction and even extensive thrombotic events are associated with *Mycoplasma pneumoniae* infection in children [118–122]. Furthermore, a recent study demonstrates that elevated D-dimer, specifically >11.1 mg/L (even >5.0 mg/L), would assist in the early diagnosis of thrombosis in MPP [123]. However, another recent study has shown that there is no statistically significant difference in D-dimer between *Mycoplasma pneumoniae* NP and non-*Mycoplasma pneumoniae* NP and even no case of pulmonary embolism was observed in NP [57]. On the other hand, higher levels of IL-6 and IgE were also observed in NP caused by MPP compared with non-NP [95,124]. And CT value of large pulmonary lesions  $\leq 36.43$  and IFN- $\gamma \leq 7.25$  pg/mL might help us to early predict NP from MPP with large pulmonary lesions in children [95].

Clinically, it is necessary to be vigilant about the possibility of NP in previously healthy and immunocompetent children with lobar pneumonia, especially when clinical manifestations, radiographic features and laboratory data like reduced serum albumin, elevated inflammatory markers and increased D-dimer do not improve or even worsen in spite of antibiotics with supportive care. If radiographic features reveal pulmonary consolidations and/or the CT value of large pulmonary lesions is  $\leq 36.43$  and/or laboratory data exceeds a certain range (WBC  $\geq 15.1 \times 10^9$ /L, CRP  $\geq 121.5$  mg/L, D-dimer > 11.1 mg/L, IFN- $\gamma \leq 7.25$  pg/mL, serum LDH  $\geq 353.5$  U/L and/or pleural fluid LDH > 1000 U/L), NP would be more suspicious. Although culture is time-consuming, analyzing drug sensitivity is still the most important thing in treating bacterial infections. In the meantime, current molecular biology methods make it possible to identify the responsible pathogen rapidly. The combination of laboratory data and certain pathogens identification like MASA and refractory *Mycoplasma pneumoniae* would help diagnose NP.

## 5. Management

### 5.1. Antibiotics and Adjunctive Therapy

To date, recommendations for the optimal management of NP rely mainly on expert opinion for the lack of high-quality randomized controlled trials. In general, the initial treatment is conservative in immunocompetent children. Intravenous (IV) antibiotics with supportive care are the mainstay of therapy. The regimen for NP needs to contain both anti-pneumococcal and anti-staphylococcal antibiotics, such as high-dose penicillin or ampicillin, amoxicillin-clavulanic acid, or second-generation or third-generation cephalosporin [1]. When coinfection with *Mycoplasma pneumoniae* is documented, a macrolide like IV azithromycin should be included in the treatment [63]. Local epidemiologic and patterns of antibiotic resistance should be taken into consideration. In areas where multidrug-resistant pneumococcus or MRSA is prevalent, vancomycin is usually added as the first-line agent before the availability of culture results [125,126]. However, a recent study showed empiric vancomycin for children predicted mortality and poor

outcomes [126]. An increased risk of nephrotoxicity has been reported in several pediatric studies [126,127]. It is difficult to reach therapeutic levels of vancomycin in children with good renal clearance, and vancomycin can penetrate poorly into lung tissues [88]. Protein synthesis inhibitors such as linezolid, clindamycin, or rifampicin may be a better alternative to vancomycin for the treatment of NP caused by PVL-positive *Staphylococcus aureus*, but their clinical evaluation is not available [128]. Antimicrobial peptides have been a hotspot of multidrug-resistant bacteria. It has been reported that  $\alpha$ -defensins can neutralize PVL and inhibit its cytotoxicity [129]. Antimicrobial peptides may be a new kind of antibiotic for NP in the future. If patients do not respond well, treatment can be tailed according to the results of antibiotic susceptibility testing [125].

For NP caused by SMPP or RMPP, the combination of macrolide and systemic corticosteroids may be an effective treatment [130]. However, there is a lack of studies to determine its effectiveness and safety. IV immunoglobulin containing pooled human polyclonal antibodies can not only modulate the immune system but also neutralize specific lung-damaging toxins. It could be considered an adjunctive therapy, but clinical studies are still rare [128,131]. To eliminate intracellular MASA, an antibody-antibiotic conjugate consisting of an anti-*Staphylococcus aureus* antibody and the rifamycin derivative rifalogue may be a novel way [132]. When *Mycobacterium tuberculosis*, viruses, or fungi are suspected, anti-tuberculosis, anti-viral, or anti-fungal therapy should be added, respectively.

### 5.2. Flexible Bronchoscopy and Surgery

Flexible fiberoptic bronchoscopy with bronchoalveolar lavage is an important modality of diagnosis and therapy in pediatric patients [133]. It can detect endobronchial abnormalities, obtain more efficient samples for bacteriologic, cytologic and histologic detection and offer therapeutic interventions [134]. Taking the opportunity to apply bronchoscopy has been shown to promote rapid recovery in refractory pneumonia, while bronchoscopy for NP has been rarely reported [76,133,135]. Chest drains, a kind of interventional procedure, are used to remove large empyema or parapneumonic effusion or pyopneumothorax in children with NP. It has been reported to have similar outcomes treating NP with surgical treatments [4]. Surgical treatments of pediatric NP are recommended in cases where there is the presence of complications or no complete response to the conservative treatment. A study found that a delay in surgery is associated with more complications and recommended an early intervention [136]. Early thoracoscopy may hasten recovery and avoid late lung resections [137]. However, postoperative complications such as BPF or small pneumatoceles are common, and surgical treatments are associated with wound infections, bleeding, prolonged pain and recovery times [136,138]. In fact, lung resection involving wedge resection or pneumonectomy in children is rare because it may impair future pulmonary function in spite of having little effect on postoperative FVC or FEV1 [139]. Most pneumatoceles can resolve spontaneously within weeks or months, while 80% of BPF in children need surgical treatments [30,140]. When fever and complications like acute respiratory failure, BPF, empyema and sepsis persist, video-assisted thoracoscopic surgery or mini-thoracotomy may be required [141]. Thoracotomy can debride fibrinous material, excise necrotic tissue, close air leaks and drain pus from the pleural cavity [137]. Endobronchial embolization, which is mainly used in adults, may be a less invasive alternative treatment for large pneumatoceles and BPF in children than the classic surgical approach [140].

## 6. Conclusions

*Streptococcus pneumoniae*, *Staphylococcus aureus* and *Mycoplasma pneumoniae* are the main infectious agents causing NP. Although detailed mechanisms are still not clear, we expect to recognize them earlier, take timely treatment measures and develop novel therapeutic strategies. Current studies focus on radiological outcomes, clinical features, laboratory characteristics and the development of testing technology. In the future, predictors from these aspects may be used in clinical.



**Author Contributions:** Y.Z. (Yuanyuan Zhang) and Y.Z. (Yunlian Zhou) conceived and designed the study in addition to critical revision of the manuscript; Y.C., L.L. and C.W. drafted the manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was partially supported by grants from the National Natural Science Foundation (81501374) and the Zhejiang Province Natural Science Foundation of China (LY18H100002).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** We thank all the authors of the studies included in this review.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- De Benedictis, F.M.; Kerem, E.; Chang, A.B.; Colin, A.A.; Zar, H.J.; Bush, A. Complicated pneumonia in children. *Lancet* **2020**, *396*, 786–798. [[CrossRef](#)] [[PubMed](#)]
- Masters, I.B.; Isles, A.F.; Grimwood, K. Necrotizing pneumonia: An emerging problem in children? *Pneumonia* **2017**, *9*, 11. [[CrossRef](#)] [[PubMed](#)]
- Lemaître, C.; Angoulvant, F.; Gabor, F.; Makhoul, J.; Bonacorsi, S.; Naudin, J.; Alison, M.; Faye, A.; Bingen, E.; Lorrot, M. Necrotizing pneumonia in children: Report of 41 cases between 2006 and 2011 in a French tertiary care center. *Pediatr. Infect. Dis. J.* **2013**, *32*, 1146–1149. [[CrossRef](#)] [[PubMed](#)]
- Sawicki, G.S.; Lu, F.L.; Valim, C.; Cleveland, R.H.; Colin, A.A. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. *Eur. Respir. J.* **2008**, *31*, 1285–1291. [[CrossRef](#)]
- Hsieh, Y.C.; Hsueh, P.R.; Lu, C.Y.; Lee, P.I.; Lee, C.Y.; Huang, L.M. Clinical manifestations and molecular epidemiology of necrotizing pneumonia and empyema caused by *Streptococcus pneumoniae* in children in Taiwan. *Clin. Infect. Dis.* **2004**, *38*, 830–835. [[CrossRef](#)]
- Ness-Cochinwala, M.; Kobaitri, K.; Totapally, B.R. Characteristics and Outcomes of Children With Necrotizing Pneumonia. *Pediatr. Crit. Care Med.* **2021**, *22*, e640–e643. [[CrossRef](#)]
- Gross, I.; Gordon, O.; Cohen-Cymbarknoh, M.; Reiter, J.; Tsabari, R.; Gileles-Hillel, A.; Erlichman, I.; Hevroni, A.; Shoseyov, D.; Kerem, E. Giant lung cysts following necrotizing pneumonia: Resolution with conservative treatment. *Pediatr. Pulmonol.* **2019**, *54*, 901–906. [[CrossRef](#)]
- Krenke, K.; Sanocki, M.; Urbankowska, E.; Kraj, G.; Krawiec, M.; Urbankowski, T.; Peradzyńska, J.; Kulus, M. Necrotizing Pneumonia and Its Complications in Children. *Adv. Exp. Med. Biol.* **2015**, *857*, 9–17. [[CrossRef](#)]
- Ozturk, Z.; Duman Kucukkuray, M.; Ozdem, S.; Cinar, H.G.; Aytakin, C.; Caglar, O. Surfactant for a Patient with Refractory Pyopneumothorax and Acute Respiratory Distress Syndrome Due to Pneumococcal Necrotizing Pneumonia Complicated by a Bronchopleural Fistula. *Pediatr. Allergy Immunol. Pulmonol.* **2022**, *35*, 120–123. [[CrossRef](#)]
- Spencer, D.A.; Thomas, M.F. Necrotising pneumonia in children. *Paediatr. Respir. Rev.* **2014**, *15*, 240–245. [[CrossRef](#)]
- Frawley, A.A.; Powell, L.; McQuiston, J.R.; Gulvik, C.A.; Begue, R.E. Necrotizing Pneumonia Caused by *Chromobacterium violaceum*: Report of a Rare Human Pathogen Causing Disease in an Immunodeficient Child. *Am. J. Trop. Med. Hyg.* **2018**, *99*, 164–167. [[CrossRef](#)] [[PubMed](#)]
- Jacobs, C.; Goussard, P.; Gie, R.P. Mycobacterium tuberculosis, a cause of necrotising pneumonia in childhood: A case series. *Int. J. Tuberc. Lung Dis.* **2018**, *22*, 614–616. [[CrossRef](#)]
- O'Brien, K.L.; Wolfson, L.J.; Watt, J.P.; Henkle, E.; Deloria-Knoll, M.; McCall, N.; Lee, E.; Mulholland, K.; Levine, O.S.; Cherian, T. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: Global estimates. *Lancet* **2009**, *374*, 893–902. [[CrossRef](#)]
- Kerem, E.; Bar Ziv, Y.; Rudenski, B.; Katz, S.; Kleid, D.; Branski, D. Bacteremic necrotizing pneumococcal pneumonia in children. *Am. J. Respir. Crit. Care Med.* **1994**, *149*, 242–244. [[CrossRef](#)]
- Hyams, C.; Camberlein, E.; Cohen, J.M.; Bax, K.; Brown, J.S. The *Streptococcus pneumoniae* capsule inhibits complement activity and neutrophil phagocytosis by multiple mechanisms. *Infect. Immun.* **2010**, *78*, 704–715. [[CrossRef](#)] [[PubMed](#)]
- Geno, K.A.; Gilbert, G.L.; Song, J.Y.; Skovsted, I.C.; Klugman, K.P.; Jones, C.; Konradsen, H.B.; Nahm, M.H. Pneumococcal Capsules and Their Types: Past, Present, and Future. *Clin. Microbiol. Rev.* **2015**, *28*, 871–899. [[CrossRef](#)]
- Feldman, C.; Anderson, R. Recent advances in our understanding of *Streptococcus pneumoniae* infection. *F1000Prime Rep.* **2014**, *6*, 82. [[CrossRef](#)]
- American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement: Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* **2000**, *106*, 362–366. [[CrossRef](#)]
- Johnson, H.L.; Deloria-Knoll, M.; Levine, O.S.; Stoszek, S.K.; Freimanis Hance, L.; Reithinger, R.; Muenz, L.R.; O'Brien, K.L. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: The pneumococcal global serotype project. *PLoS Med.* **2010**, *7*, e1000378. [[CrossRef](#)] [[PubMed](#)]

20. Bender, J.M.; Ampofo, K.; Korgenski, K.; Daly, J.; Pavia, A.T.; Mason, E.O.; Byington, C.L. Pneumococcal necrotizing pneumonia in Utah: Does serotype matter? *Clin. Infect. Dis.* **2008**, *46*, 1346–1352. [[CrossRef](#)]
21. Díaz-Conradi, A.; Hernández, S.; García-García, J.J.; Muñoz-Almagro, C.; Moraga-Llop, F.; Ciruela, P.; Izquierdo, C.; Campins, M.; de Sevilla, M.F.; González-Peris, S.; et al. Complicated pneumococcal pneumonia with pleural effusion or empyema in the 13-valent pneumococcal conjugate vaccine era. *Pediatr. Pulmonol.* **2019**, *54*, 517–524. [[CrossRef](#)] [[PubMed](#)]
22. Azzari, C.; Serranti, D.; Nieddu, F.; Moriondo, M.; Casini, A.; Lodi, L.; de Benedictis, F.M.; De Vitis, E.; Cavone, F.; Cortimiglia, M.; et al. Significant impact of pneumococcal conjugate vaccination on pediatric parapneumonic effusion: Italy 2006–2018. *Vaccine* **2019**, *37*, 2704–2711. [[CrossRef](#)] [[PubMed](#)]
23. Carloni, I.; Ricci, S.; Rubino, C.; Cobellis, G.; Rinaldelli, G.; Azzari, C.; de Benedictis, F.M. Necrotizing pneumonia among Italian children in the pneumococcal conjugate vaccine era. *Pediatr. Pulmonol.* **2021**, *56*, 1127–1135. [[CrossRef](#)] [[PubMed](#)]
24. Gonzalez-Peris, S.; Campins, M.; Garcia-Garcia, J.J.; Diaz-Conradi, A.; Dominguez, A.; Ciruela, P.; de Sevilla, M.F.; Hernandez, S.; Munoz-Almagro, C.; Izquierdo, C.; et al. Necrotizing pneumonia due to *Streptococcus pneumoniae* in children during the period of non-systematic use of PCV13 in Catalonia, Spain. *Enferm. Infecc. Microbiol. Clin. Engl. Ed.* **2021**, *39*, 486–492. [[CrossRef](#)] [[PubMed](#)]
25. Ratner, A.J.; Hippe, K.R.; Aguilar, J.L.; Bender, M.H.; Nelson, A.L.; Weiser, J.N. Epithelial cells are sensitive detectors of bacterial pore-forming toxins. *J. Biol. Chem.* **2006**, *281*, 12994–12998. [[CrossRef](#)] [[PubMed](#)]
26. Hoffmann, E.; Dittrich-Breiholz, O.; Holtmann, H.; Kracht, M. Multiple control of interleukin-8 gene expression. *J. Leukoc. Biol.* **2002**, *72*, 847–855. [[CrossRef](#)] [[PubMed](#)]
27. Mitchell, T.J.; Andrew, P.W.; Saunders, F.K.; Smith, A.N.; Boulnois, G.J. Complement activation and antibody binding by pneumolysin via a region of the toxin homologous to a human acute-phase protein. *Mol. Microbiol.* **1991**, *5*, 1883–1888. [[CrossRef](#)]
28. Hirst, R.A.; Kadioglu, A.; O’Callaghan, C.; Andrew, P.W. The role of pneumolysin in pneumococcal pneumonia and meningitis. *Clin. Exp. Immunol.* **2004**, *138*, 195–201. [[CrossRef](#)]
29. Kirkham, L.A.; Jefferies, J.M.; Kerr, A.R.; Jing, Y.; Clarke, S.C.; Smith, A.; Mitchell, T.J. Identification of invasive serotype 1 pneumococcal isolates that express nonhemolytic pneumolysin. *J. Clin. Microbiol.* **2006**, *44*, 151–159. [[CrossRef](#)]
30. Hsieh, Y.C.; Wang, C.W.; Lai, S.H.; Lai, J.Y.; Wong, K.S.; Huang, Y.C.; Chang, K.Y.; Chiu, C.H.; Lin, T.Y. Necrotizing pneumococcal pneumonia with bronchopleural fistula among children in Taiwan. *Pediatr. Infect. Dis. J.* **2011**, *30*, 740–744. [[CrossRef](#)]
31. Hsieh, Y.C.; Chi, H.; Chang, K.Y.; Lai, S.H.; Mu, J.J.; Wong, K.S.; Liu, C.C.; Huang, Y.C.; Lin, H.C.; Chang, L.Y.; et al. Increase in fitness of *Streptococcus pneumoniae* is associated with the severity of necrotizing pneumonia. *Pediatr. Infect. Dis. J.* **2015**, *34*, 499–505. [[CrossRef](#)] [[PubMed](#)]
32. Ensínck, G.; Lazarte, G.; Ernst, A.; Romagnoli, A.; Lopez Papucci, S.; Aletti, A.; Chiossone, A.; Pigozzi, F.; Sguassero, Y. Community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia in a children’s hospital. Our ten-year experience. *Arch. Argent. Pediatr.* **2021**, *119*, 11–17. [[CrossRef](#)]
33. Ritz, N.; Curtis, N. The role of Panton-Valentine leukocidin in *Staphylococcus aureus* musculoskeletal infections in children. *Pediatr. Infect. Dis. J.* **2012**, *31*, 514–518. [[CrossRef](#)]
34. Badiou, C.; Dumitrescu, O.; George, N.; Forbes, A.R.; Drougka, E.; Chan, K.S.; Ramdani-Bouguessa, N.; Meugnier, H.; Bes, M.; Vandenesch, F.; et al. Rapid detection of *Staphylococcus aureus* Panton-Valentine leukocidin in clinical specimens by enzyme-linked immunosorbent assay and immunochromatographic tests. *J. Clin. Microbiol.* **2010**, *48*, 1384–1390. [[CrossRef](#)]
35. Gillet, Y.; Issartel, B.; Vanhems, P.; Fournet, J.-C.; Lina, G.; Bes, M.; Vandenesch, F.; Piémont, Y.; Brousse, N.; Floret, D.; et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* **2002**, *359*, 753–759. [[CrossRef](#)]
36. König, B.; Prévost, G.; Piémont, Y.; König, W. Effects of *Staphylococcus aureus* leukocidins on inflammatory mediator release from human granulocytes. *J. Infect. Dis.* **1995**, *171*, 607–613. [[CrossRef](#)] [[PubMed](#)]
37. Szmigielski, S.; Prevost, G.; Monteil, H.; Colin, D.A.; Jeljaszewicz, J. Leukocidal toxins of staphylococci. *Zentralbl Bakteriell* **1999**, *289*, 185–201. [[CrossRef](#)] [[PubMed](#)]
38. Diep, B.A.; Chan, L.; Tattevin, P.; Kajikawa, O.; Martin, T.R.; Basuino, L.; Mai, T.T.; Marbach, H.; Braughton, K.R.; Whitney, A.R.; et al. Polymorphonuclear leukocytes mediate *Staphylococcus aureus* Panton-Valentine leukocidin-induced lung inflammation and injury. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5587–5592. [[CrossRef](#)] [[PubMed](#)]
39. Chow, S.H.; Deo, P.; Yeung, A.T.Y.; Kostoulias, X.P.; Jeon, Y.; Gao, M.L.; Seidi, A.; Olivier, F.A.B.; Sridhar, S.; Nethercott, C.; et al. Targeting NLRP3 and Staphylococcal pore-forming toxin receptors in human-induced pluripotent stem cell-derived macrophages. *J. Leukoc. Biol.* **2020**, *108*, 967–981. [[CrossRef](#)]
40. Harada, S.; Kawada, H.; Maehana, S.; Matsui, H.; Kubo, M.; Kojima, F.; Kitasato, H.; Katagiri, M. Panton-Valentine Leukocidin Induces Cytokine Release and Cytotoxicity Mediated by the C5a Receptor on Rabbit Alveolar Macrophages. *Jpn. J. Infect. Dis.* **2021**, *74*, 352–358. [[CrossRef](#)]
41. Diep, B.A.; Hilliard, J.J.; Le, V.T.; Tkaczyk, C.; Le, H.N.; Tran, V.G.; Rao, R.L.; Dip, E.C.; Pereira-Franchi, E.P.; Cha, P.; et al. Targeting Alpha Toxin To Mitigate Its Lethal Toxicity in Ferret and Rabbit Models of *Staphylococcus aureus* Necrotizing Pneumonia. *Antimicrob. Agents Chemother.* **2017**, *61*, e02456-16. [[CrossRef](#)]
42. Kebaier, C.; Chamberland, R.R.; Allen, I.C.; Gao, X.; Broglie, P.M.; Hall, J.D.; Jania, C.; Doerschuk, C.M.; Tilley, S.L.; Duncan, J.A. *Staphylococcus aureus* alpha-hemolysin mediates virulence in a murine model of severe pneumonia through activation of the NLRP3 inflammasome. *J. Infect. Dis.* **2012**, *205*, 807–817. [[CrossRef](#)]

43. Parimon, T.; Li, Z.; Bolz, D.D.; McIndoo, E.R.; Bayer, C.R.; Stevens, D.L.; Bryant, A.E. Staphylococcus aureus alpha-hemolysin promotes platelet-neutrophil aggregate formation. *J. Infect. Dis.* **2013**, *208*, 761–770. [[CrossRef](#)] [[PubMed](#)]
44. Kitur, K.; Parker, D.; Nieto, P.; Ahn, D.S.; Cohen, T.S.; Chung, S.; Wachtel, S.; Bueno, S.; Prince, A. Toxin-induced necroptosis is a major mechanism of Staphylococcus aureus lung damage. *PLoS Pathog.* **2015**, *11*, e1004820. [[CrossRef](#)] [[PubMed](#)]
45. Strandberg, K.L.; Rotschafer, J.H.; Vetter, S.M.; Buonpane, R.A.; Kranz, D.M.; Schlievert, P.M. Staphylococcal superantigens cause lethal pulmonary disease in rabbits. *J. Infect. Dis.* **2010**, *202*, 1690–1697. [[CrossRef](#)]
46. Spaulding, A.R.; Salgado-Pabon, W.; Kohler, P.L.; Horswill, A.R.; Leung, D.Y.; Schlievert, P.M. Staphylococcal and streptococcal superantigen exotoxins. *Clin. Microbiol. Rev.* **2013**, *26*, 422–447. [[CrossRef](#)]
47. Gonzalez, B.E.; Hulten, K.G.; Dishop, M.K.; Lamberth, L.B.; Hammerman, W.A.; Mason, E.O., Jr.; Kaplan, S.L. Pulmonary manifestations in children with invasive community-acquired Staphylococcus aureus infection. *Clin. Infect. Dis.* **2005**, *41*, 583–590. [[CrossRef](#)]
48. Labandeira-Rey, M.; Couzon, F.; Boisset, S.; Brown, E.L.; Bes, M.; Benito, Y.; Barbu, E.M.; Vazquez, V.; Höök, M.; Etienne, J.; et al. Staphylococcus aureus Panton-Valentine leukocidin causes necrotizing pneumonia. *Science* **2007**, *315*, 1130–1133. [[CrossRef](#)] [[PubMed](#)]
49. O'Brien, L.; Kerrigan, S.W.; Kaw, G.; Hogan, M.; Penadés, J.; Litt, D.; Fitzgerald, D.J.; Foster, T.J.; Cox, D. Multiple mechanisms for the activation of human platelet aggregation by Staphylococcus aureus: Roles for the clumping factors ClfA and ClfB, the serine-aspartate repeat protein SdrE and protein A. *Mol. Microbiol.* **2002**, *44*, 1033–1044. [[CrossRef](#)]
50. Li, C.; Wu, Y.; Riehle, A.; Ma, J.; Kamler, M.; Gulbins, E.; Grassme, H. Staphylococcus aureus Survives in Cystic Fibrosis Macrophages, Forming a Reservoir for Chronic Pneumonia. *Infect. Immun.* **2017**, *85*, e00883-16. [[CrossRef](#)]
51. Stelzner, K.; Winkler, A.C.; Liang, C.; Boyny, A.; Ade, C.P.; Dandekar, T.; Fraunholz, M.J.; Rudel, T. Intracellular Staphylococcus aureus Perturbs the Host Cell Ca(2+) Homeostasis To Promote Cell Death. *mBio* **2020**, *11*, e02250-20. [[CrossRef](#)]
52. Von Hoven, G.; Rivas, A.J.; Neukirch, C.; Klein, S.; Hamm, C.; Qin, Q.; Meyenburg, M.; Füser, S.; Saftig, P.; Hellmann, N.; et al. Dissecting the role of ADAM10 as a mediator of Staphylococcus aureus  $\alpha$ -toxin action. *Biochem J.* **2016**, *473*, 1929–1940. [[CrossRef](#)]
53. Eichstaedt, S.; Gäbler, K.; Below, S.; Müller, C.; Kohler, C.; Engelmann, S.; Hildebrandt, P.; Völker, U.; Hecker, M.; Hildebrandt, J.P. Effects of Staphylococcus aureus-hemolysin A on calcium signalling in immortalized human airway epithelial cells. *Cell Calcium* **2009**, *45*, 165–176. [[CrossRef](#)] [[PubMed](#)]
54. Jain, S.; Williams, D.J.; Arnold, S.R.; Ampofo, K.; Bramley, A.M.; Reed, C.; Stockmann, C.; Anderson, E.J.; Grijalva, C.G.; Self, W.H.; et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N. Engl. J. Med.* **2015**, *372*, 835–845. [[CrossRef](#)] [[PubMed](#)]
55. Shin, E.J.; Kim, Y.; Jeong, J.Y.; Jung, Y.M.; Lee, M.H.; Chung, E.H. The changes of prevalence and etiology of pediatric pneumonia from National Emergency Department Information System in Korea, between 2007 and 2014. *Korean J. Pediatr.* **2018**, *61*, 291–300. [[CrossRef](#)] [[PubMed](#)]
56. Wang, X.; Zhong, L.J.; Chen, Z.M.; Zhou, Y.L.; Ye, B.; Zhang, Y.Y. Necrotizing pneumonia caused by refractory Mycoplasma pneumonia pneumonia in children. *World J. Pediatr.* **2018**, *14*, 344–349. [[CrossRef](#)] [[PubMed](#)]
57. Yang, B.L.; Zhang, W.L.; Gu, W.J.; Zhang, X.X.; Wang, M.J.; Huang, L.; Zhu, C.H.; Yan, Y.D.; Ji, W.; Ni, H.P.; et al. Differences of clinical features and prognosis between Mycoplasma pneumoniae necrotizing pneumonia and non-Mycoplasma pneumoniae necrotizing pneumonia in children. *BMC Infect. Dis.* **2021**, *21*, 797. [[CrossRef](#)] [[PubMed](#)]
58. Lee, K.L.; Lee, C.M.; Yang, T.L.; Yen, T.Y.; Chang, L.Y.; Chen, J.M.; Lee, P.I.; Huang, L.M.; Lu, C.Y. Severe Mycoplasma pneumoniae pneumonia requiring intensive care in children, 2010–2019. *J. Formos Med. Assoc.* **2021**, *120*, 281–291. [[CrossRef](#)] [[PubMed](#)]
59. Zhu, Z.; Zhang, T.; Guo, W.; Ling, Y.; Tian, J.; Xu, Y. Clinical characteristics of refractory mycoplasma pneumoniae pneumonia in children treated with glucocorticoid pulse therapy. *BMC Infect. Dis.* **2021**, *21*, 126. [[CrossRef](#)]
60. Lee, H.; Yun, K.W.; Lee, H.J.; Choi, E.H. Antimicrobial therapy of macrolide-resistant Mycoplasma pneumoniae pneumonia in children. *Expert Rev. Anti. Infect. Ther.* **2018**, *16*, 23–34. [[CrossRef](#)]
61. Chen, Y.C.; Hsu, W.Y.; Chang, T.H. Macrolide-Resistant Mycoplasma pneumoniae Infections in Pediatric Community-Acquired Pneumonia. *Emerg. Infect. Dis.* **2020**, *26*, 1382–1391. [[CrossRef](#)]
62. Zhou, Y.; Wang, J.; Chen, W.; Shen, N.; Tao, Y.; Zhao, R.; Luo, L.; Li, B.; Cao, Q. Impact of viral coinfection and macrolide-resistant mycoplasma infection in children with refractory Mycoplasma pneumoniae pneumonia. *BMC Infect. Dis.* **2020**, *20*, 633. [[CrossRef](#)]
63. Wang, Y.; Xu, D.; Li, S.; Chen, Z. Mycoplasma pneumoniae-associated necrotizing pneumonitis in children. *Pediatr. Int.* **2012**, *54*, 293–297. [[CrossRef](#)]
64. Somerson, N.L.; Walls, B.E.; Chanock, R.M. Hemolysin of Mycoplasma pneumoniae: Tentative identification as a peroxide. *Science* **1965**, *150*, 226–228. [[CrossRef](#)]
65. Kannan, T.R.; Baseman, J.B. ADP-ribosylating and vacuolating cytotoxin of Mycoplasma pneumoniae represents unique virulence determinant among bacterial pathogens. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 6724–6729. [[CrossRef](#)] [[PubMed](#)]
66. Segovia, J.A.; Chang, T.H.; Winter, V.T.; Coalson, J.J.; Cagle, M.P.; Pandranki, L.; Bose, S.; Baseman, J.B.; Kannan, T.R. NLRP3 Is a Critical Regulator of Inflammation and Innate Immune Cell Response during Mycoplasma pneumoniae Infection. *Infect. Immun* **2018**, *86*, e00548-17. [[CrossRef](#)] [[PubMed](#)]
67. Luo, H.; He, J.; Qin, L.; Chen, Y.; Chen, L.; Li, R.; Zeng, Y.; Zhu, C.; You, X.; Wu, Y. Mycoplasma pneumoniae lipids license TLR-4 for activation of NLRP3 inflammasome and autophagy to evoke a proinflammatory response. *Clin. Exp. Immunol.* **2021**, *203*, 66–79. [[CrossRef](#)]

68. Blötz, C.; Stülke, J. Glycerol metabolism and its implication in virulence in Mycoplasma. *FEMS Microbiol. Rev.* **2017**, *41*, 640–652. [[CrossRef](#)] [[PubMed](#)]
69. Almagor, M.; Kahane, I.; Yatziv, S. Role of superoxide anion in host cell injury induced by mycoplasma pneumoniae infection. A study in normal and trisomy 21 cells. *J. Clin. Invest.* **1984**, *73*, 842–847. [[CrossRef](#)]
70. Angelova, P.R.; Horrocks, M.H.; Klenerman, D.; Gandhi, S.; Abramov, A.Y.; Shchepinov, M.S. Lipid peroxidation is essential for  $\alpha$ -synuclein-induced cell death. *J. Neurochem.* **2015**, *133*, 582–589. [[CrossRef](#)]
71. Li, F.; Zhang, Y.; Shi, P.; Cao, L.; Su, L.; Fu, P.; Abuduxikuer, K.; Wang, L.; Wang, Y.; Lu, R.; et al. Mycoplasma pneumoniae and Adenovirus Coinfection Cause Pediatric Severe Community-Acquired Pneumonia. *Microbiol. Spectr.* **2022**, *10*, e0002622. [[CrossRef](#)]
72. Choo, S.; Lee, Y.Y.; Lee, E. Clinical significance of respiratory virus coinfection in children with Mycoplasma pneumoniae pneumonia. *BMC Pulm. Med.* **2022**, *22*, 212. [[CrossRef](#)]
73. Zhou, Y.L.; Liu, J.R.; Yi, Q.W.; Chen, L.N.; Han, Z.Y.; Xu, C.D.; Liu, S.Y.; Hao, C.L.; Liu, J.; Li, Q.L.; et al. [A multicenter retrospective study on the etiology of necrotizing pneumonia in children]. *Zhonghua Er Ke Za Zhi* **2021**, *59*, 658–664. [[CrossRef](#)] [[PubMed](#)]
74. Wenzel, J.J.; Hentschel, J.; Silvis, W.; Permanetter, W.; Mattes, J.; Kochanowski, B.; Herterich, R.; Jilg, W.; Linde, H.J. Rapidly fatal necrotizing pneumonia in a 12-year-old boy caused by co-infection with parainfluenza virus type 1 and Pantone-Valentine leukocidin (PVL)-positive methicillin-sensitive Staphylococcus aureus. *Infection* **2009**, *37*, 75–77. [[CrossRef](#)]
75. Barrett, N.A.; Armstrong-James, D.; Edgeworth, J.; Wyncoll, D. Novel H1N1 influenza and Pantone-Valentine leukocidin Staphylococcus aureus necrotizing pneumonia. *Br. J. Hosp. Med.* **2010**, *71*, 350–351. [[CrossRef](#)] [[PubMed](#)]
76. Han, C.; Zhang, T.; Zhao, Y.; Dong, L.; Li, X.; Zheng, J.; Guo, W.; Xu, Y.; Cai, C. Successful treatment of pleural empyema and necrotizing pneumonia caused by methicillin-resistant Staphylococcus aureus infection following influenza A virus infection: A case report and literature review. *Front. Pediatr.* **2022**, *10*, 959419. [[CrossRef](#)] [[PubMed](#)]
77. Arruda, A.A.; Fortuna, J.P.; Raposo, A.T.; Soares, M.R.P.; Goncalves, J.A.; Gomes, M.F. Influenza virus infection complicated by bacterial necrotising pneumonia: Two case reports. *Paediatr. Int. Child. Health* **2020**, *40*, 202–206. [[CrossRef](#)] [[PubMed](#)]
78. Yazer, J.; Giacomantonio, M.; Macdonald, N.; Lopushinsky, S. Severe necrotizing pneumonia in a child with pandemic (H1N1) influenza. *Cmaj* **2011**, *183*, 215–219. [[CrossRef](#)]
79. Peltola, V.T.; McCullers, J.A. Respiratory viruses predisposing to bacterial infections: Role of neuraminidase. *Pediatr. Infect. Dis. J.* **2004**, *23*, S87–S97. [[CrossRef](#)]
80. Rudd, J.M.; Ashar, H.K.; Chow, V.T.; Teluguakula, N. Lethal Synergism between Influenza and Streptococcus pneumoniae. *J. Infect. Pulm Dis.* **2016**, *2*, 114. [[CrossRef](#)]
81. Giamarellos-Bourboulis, E.J.; Raftogiannis, M.; Antonopoulou, A.; Baziaka, F.; Koutoukas, P.; Savva, A.; Kanni, T.; Georgitsi, M.; Pistiki, A.; Tsaganos, T.; et al. Effect of the novel influenza A (H1N1) virus in the human immune system. *PLoS ONE* **2009**, *4*, e8393. [[CrossRef](#)]
82. Niemann, S.; Ehrhardt, C.; Medina, E.; Warnking, K.; Tuschscherr, L.; Heitmann, V.; Ludwig, S.; Peters, G.; Löffler, B. Combined action of influenza virus and Staphylococcus aureus pantone-valentine leukocidin provokes severe lung epithelium damage. *J. Infect. Dis.* **2012**, *206*, 1138–1148. [[CrossRef](#)] [[PubMed](#)]
83. Chandler, J.D.; Hu, X.; Ko, E.J.; Park, S.; Lee, Y.T.; Orr, M.; Fernandes, J.; Uppal, K.; Kang, S.M.; Jones, D.P.; et al. Metabolic pathways of lung inflammation revealed by high-resolution metabolomics (HRM) of H1N1 influenza virus infection in mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2016**, *311*, R906–R916. [[CrossRef](#)] [[PubMed](#)]
84. Ayari, A.; Rosa-Calatrava, M.; Lancel, S.; Barthelemy, J.; Pizzorno, A.; Mayeuf-Louchart, A.; Baron, M.; Hot, D.; Deruyter, L.; Soulard, D.; et al. Influenza infection rewires energy metabolism and induces browning features in adipose cells and tissues. *Commun. Biol.* **2020**, *3*, 237. [[CrossRef](#)]
85. Li, Q.L.; Zhang, X.Y.; Chen, B.; Ji, Y.G.; Chen, W.; Cai, S.J.; Xu, M.; Yu, M.W.; Bao, Q.Y.; Li, C.C.; et al. Early predictors of lung necrosis severity in children with community-acquired necrotizing pneumonia. *Pediatr. Pulmonol.* **2022**, *57*, 2172–2179. [[CrossRef](#)]
86. Gillet, Y.; Vanhems, P.; Lina, G.; Bes, M.; Vandenesch, F.; Floret, D.; Etienne, J. Factors predicting mortality in necrotizing community-acquired pneumonia caused by Staphylococcus aureus containing Pantone-Valentine leukocidin. *Clin. Infect. Dis.* **2007**, *45*, 315–321. [[CrossRef](#)]
87. Lease, E.D.; Alexander, B.D. Fungal diagnostics in pneumonia. *Semin Respir. Crit. Care Med.* **2011**, *32*, 663–672. [[CrossRef](#)] [[PubMed](#)]
88. Randolph, A.G.; Xu, R.; Novak, T.; Newhams, M.M.; Bubeck-Wardenburg, J.; Weiss, S.L.; Sanders, R.C.; Thomas, N.J.; Hall, M.W.; Tarquinio, K.M.; et al. Vancomycin Monotherapy May Be Insufficient to Treat Methicillin-resistant Staphylococcus aureus Coinfection in Children With Influenza-related Critical Illness. *Clin. Infect. Dis.* **2019**, *68*, 365–372. [[CrossRef](#)]
89. Wang, R.S.; Wang, S.Y.; Hsieh, K.S.; Chiou, Y.H.; Huang, I.F.; Cheng, M.F.; Chiou, C.C. Necrotizing pneumonitis caused by Mycoplasma pneumoniae in pediatric patients: Report of five cases and review of literature. *Pediatr. Infect. Dis. J.* **2004**, *23*, 564–567. [[CrossRef](#)]
90. Donnelly, L.F.; Klosterman, L.A. Cavitory necrosis complicating pneumonia in children: Sequential findings on chest radiography. *AJR Am. J. Roentgenol.* **1998**, *171*, 253–256. [[CrossRef](#)]
91. Hallifax, R.J.; Talwar, A.; Wrightson, J.M.; Edey, A.; Gleeson, F.V. State-of-the-art: Radiological investigation of pleural disease. *Respir Med.* **2017**, *124*, 88–99. [[CrossRef](#)] [[PubMed](#)]

92. Carrard, J.; Bacher, S.; Rochat-Guignard, I.; Knebel, J.F.; Alamo, L.; Meuwly, J.Y.; Tenisch, E. Necrotizing pneumonia in children: Chest computed tomography vs. lung ultrasound. *Front. Pediatr.* **2022**, *10*, 898402. [[CrossRef](#)]
93. Lai, S.H.; Wong, K.S.; Liao, S.L. Value of Lung Ultrasonography in the Diagnosis and Outcome Prediction of Pediatric Community-Acquired Pneumonia with Necrotizing Change. *PLoS ONE* **2015**, *10*, e0130082. [[CrossRef](#)] [[PubMed](#)]
94. Odev, K.; Guler, I.; Altinok, T.; Pekcan, S.; Batur, A.; Ozbiner, H. Cystic and cavitory lung lesions in children: Radiologic findings with pathologic correlation. *J. Clin. Imaging Sci.* **2013**, *3*, 60. [[CrossRef](#)]
95. Zhou, Y.; Hu, M.; Ye, B.; Chen, Z.; Zhang, Y. Early prediction of necrotizing pneumonia from mycoplasma pneumoniae pneumonia with large pulmonary lesions in children. *Sci. Rep.* **2020**, *10*, 19061. [[CrossRef](#)] [[PubMed](#)]
96. Chen, X.; Li, W.; Wang, F.; He, L.; Liu, E. Early recognition of necrotizing pneumonia in children based on non-contrast-enhanced computed tomography radiomics signatures. *Transl. Pediatr.* **2021**, *10*, 1542–1551. [[CrossRef](#)] [[PubMed](#)]
97. Immonen, E.; Wong, J.; Nieminen, M.; Kekkonen, L.; Roine, S.; Tornroos, S.; Lanca, L.; Guan, F.; Metsala, E. The use of deep learning towards dose optimization in low-dose computed tomography: A scoping review. *Radiography* **2022**, *28*, 208–214. [[CrossRef](#)]
98. Gill, M.K.; Vijayanathan, A.; Kumar, G.; Jayarani, K.; Ng, K.H.; Sun, Z. Use of 100 kV versus 120 kV in computed tomography pulmonary angiography in the detection of pulmonary embolism: Effect on radiation dose and image quality. *Quant. Imaging Med. Surg.* **2015**, *5*, 524–533. [[CrossRef](#)] [[PubMed](#)]
99. Bellizzi, A.; Bezzina, P.; Zarb, F. Optimisation of the CT pulmonary angiogram (CTPA) protocol using a low kV technique combined with high iterative reconstruction (IR): A phantom study. *Radiography* **2023**, *29*, 313–318. [[CrossRef](#)]
100. Thongprayoon, C.; Cheungpasitporn, W.; Chewcharat, A.; Mao, M.A.; Thirunavukkarasu, S.; Kashani, K.B. Impacts of admission serum albumin levels on short-term and long-term mortality in hospitalized patients. *QJM* **2020**, *113*, 393–398. [[CrossRef](#)]
101. Bekhit, O.E.; Yousef, R.M.; Abdelrasol, H.A.; Mohammed, M.A. Serum Albumin Level as a Predictor of Outcome in Patients Admitted to Pediatric Intensive Care Units. *Pediatr. Emerg. Care* **2021**, *37*, e855–e860. [[CrossRef](#)]
102. Liu, S.-S.; Song, L.-J.; Meng, F.-Z.; Peng, L.; Liu, Y.-H. Early predictors of necrotizing pneumonia in children. *Chin. J. Contemp. Pediatr.* **2016**, *18*, 391–395.
103. Rydell-Tormanen, K.; Uller, L.; Erjefalt, J.S. Direct evidence of secondary necrosis of neutrophils during intense lung inflammation. *Eur. Respir J.* **2006**, *28*, 268–274. [[CrossRef](#)] [[PubMed](#)]
104. Ulloa-Gutierrez, R. Pneumococcal necrotizing pneumonia and pleural fluid lactate dehydrogenase level. *Clin. Infect. Dis.* **2008**, *47*, 729–730. [[CrossRef](#)]
105. Klein, P.J.; Bulla, M.; Newman, R.A.; Müller, P.; Uhlenbruck, G.; Schaefer, H.E.; Krüger, G.; Fisher, R. Thomsen-Friedenreich antigen in haemolytic-uraemic syndrome. *Lancet* **1977**, *2*, 1024–1025. [[CrossRef](#)] [[PubMed](#)]
106. Chang, C.J.; Chiu, N.C.; Huang, F.Y.; Tsung-Ning Huang, D.; Chang, L.; Huang, C.Y.; Kung, Y.H.; Chi, H. Predictive value of Thomsen-Friedenreich antigen activation for Streptococcus pneumoniae infection and severity in pediatric lobar pneumonia. *J. Microbiol. Immunol. Infect.* **2019**, *52*, 571–577. [[CrossRef](#)]
107. Janapatla, R.P.; Hsu, M.H.; Liao, W.T.; Chien, K.Y.; Lee, H.Y.; Chiu, C.H. Low Serum Fetuin-A as a Biomarker to Predict Pneumococcal Necrotizing Pneumonia and Hemolytic Uremic Syndrome in Children. *Medicine* **2016**, *95*, e3221. [[CrossRef](#)]
108. Sicot, N.; Khanafer, N.; Meyssonier, V.; Dumitrescu, O.; Tristan, A.; Bes, M.; Lina, G.; Vandenesch, F.; Vanhems, P.; Etienne, J.; et al. Methicillin resistance is not a predictor of severity in community-acquired Staphylococcus aureus necrotizing pneumonia—results of a prospective observational study. *Clin. Microbiol. Infect.* **2013**, *19*, E142–E148. [[CrossRef](#)]
109. Oishi, K.; Baba, T.; Nakatomi, Y.; Ito, T.; Hiramatsu, K. A latex agglutination assay for specific detection of Pantone-Valentine leukocidin. *J. Microbiol. Methods* **2008**, *75*, 411–415. [[CrossRef](#)]
110. Johnsson, D.; Mölling, P.; Strålin, K.; Söderquist, B. Detection of Pantone-Valentine leukocidin gene in Staphylococcus aureus by LightCycler PCR: Clinical and epidemiological aspects. *Clin. Microbiol. Infect.* **2004**, *10*, 884–889. [[CrossRef](#)]
111. Senok, A.; Monecke, S.; Nassar, R.; Celiloglu, H.; Thyagarajan, S.; Muller, E.; Ehrlich, R. Lateral Flow Immunoassay for the Detection of Pantone-Valentine Leukocidin in Staphylococcus aureus From Skin and Soft Tissue Infections in the United Arab Emirates. *Front. Cell Infect. Microbiol.* **2021**, *11*, 754523. [[CrossRef](#)] [[PubMed](#)]
112. Monecke, S.; Muller, E.; Buechler, J.; Rejman, J.; Stieber, B.; Akpaka, P.E.; Bandt, D.; Burris, R.; Coombs, G.; Hidalgo-Arroyo, G.A.; et al. Rapid detection of Pantone-Valentine leukocidin in Staphylococcus aureus cultures by use of a lateral flow assay based on monoclonal antibodies. *J. Clin. Microbiol.* **2013**, *51*, 487–495. [[CrossRef](#)] [[PubMed](#)]
113. Bittar, F.; Ouchenane, Z.; Smati, F.; Raoult, D.; Rolain, J.M. MALDI-TOF-MS for rapid detection of staphylococcal Pantone-Valentine leukocidin. *Int J. Antimicrob Agents* **2009**, *34*, 467–470. [[CrossRef](#)]
114. Ambroggio, L.; Florin, T.A.; Shah, S.S.; Ruddy, R.; Yeomans, L.; Trexel, J.; Stringer, K.A. Emerging Biomarkers of Illness Severity: Urinary Metabolites Associated with Sepsis and Necrotizing Methicillin-Resistant Staphylococcus aureus Pneumonia. *Pharmacotherapy* **2017**, *37*, 1033–1042. [[CrossRef](#)]
115. Weitz, J.I.; Fredenburgh, J.C.; Eikelboom, J.W. A Test . . . in Context: D-Dimer. *J. Am. Coll. Cardiol.* **2017**, *70*, 2411–2420. [[CrossRef](#)]
116. Zheng, Y.; Hua, L.; Zhao, Q.; Li, M.; Huang, M.; Zhou, Y.; Wang, Y.; Chen, Z.; Zhang, Y. The Level of D-Dimer Is Positively Correlated With the Severity of Mycoplasma pneumoniae Pneumonia in Children. *Front. Cell Infect. Microbiol.* **2021**, *11*, 687391. [[CrossRef](#)] [[PubMed](#)]
117. Zheng, B.Y.; Zhao, J.; Cao, L. The clinical characteristics and risk factors for necrotizing pneumonia caused by Mycoplasma pneumoniae in children. *BMC Infect. Dis.* **2020**, *20*, 6. [[CrossRef](#)] [[PubMed](#)]

118. Chen, S.; Ding, Y.; Vinturache, A.; Gu, H.; Lu, M.; Ding, G. Pulmonary embolism associated with mycoplasma in a child. *Lancet Infect. Dis.* **2020**, *20*, 1347. [[CrossRef](#)]
119. Mele, N.; Turc, G. Stroke Associated With Recent Mycoplasma Pneumoniae Infection: A Systematic Review of Clinical Features and Presumed Pathophysiological Mechanisms. *Front Neurol.* **2018**, *9*, 1109. [[CrossRef](#)]
120. Pachet, A.; Dumestre-Perard, C.; Moine, M.; Marlu, R.; Rubio, A.; Bost-Bru, C. Splenic infarction associated with transient anti-prothrombin antibodies is a rare manifestation of acute Mycoplasma pneumoniae infection. *Arch. Pediatr.* **2019**, *26*, 483–486. [[CrossRef](#)]
121. Park, S.J.; Pai, K.S.; Kim, A.R.; Lee, J.H.; Shin, J.I.; Lee, S.Y. Fulminant and Fatal Multiple Organ Failure in a 12-Year-Old Boy With Mycoplasma pneumoniae Infection. *Allergy Asthma Immunol. Res.* **2012**, *4*, 55–57. [[CrossRef](#)]
122. Hahn, D.W.; Atkinson, C.E.; Le, M. Multiple anatomic sites of infarction in a pediatric patient with M. pneumoniae infection, a case report. *BMC Pediatr.* **2021**, *21*, 372. [[CrossRef](#)] [[PubMed](#)]
123. Liu, J.; He, R.; Wu, R.; Wang, B.; Xu, H.; Zhang, Y.; Li, H.; Zhao, S. Mycoplasma pneumoniae pneumonia associated thrombosis at Beijing Children's hospital. *BMC Infect Dis.* **2020**, *20*, 51. [[CrossRef](#)] [[PubMed](#)]
124. Zhou, L.L.; Li, Y.; Xu, Z.F.; Peng, X.Y.; Gong, X.Y.; Yang, L. Increased Total Serum Immunoglobulin E Is Likely to Cause Complications of Mycoplasma pneumoniae Pneumonia in Children. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 783635. [[CrossRef](#)] [[PubMed](#)]
125. Lu, S.; Tsai, J.D.; Tsao, T.F.; Liao, P.F.; Sheu, J.N. Necrotizing pneumonia and acute purulent pericarditis caused by Streptococcus pneumoniae serotype 19A in a healthy 4-year-old girl after one catch-up dose of 13-valent pneumococcal conjugate vaccine. *Paediatr. Int. Child Health* **2016**, *36*, 235–239. [[CrossRef](#)]
126. Campbell, A.J.; Al Yazidi, L.S.; Phuong, L.K.; Leung, C.; Best, E.J.; Webb, R.H.; Voss, L.; Athan, E.; Britton, P.N.; Bryant, P.A.; et al. Pediatric Staphylococcus aureus Bacteremia: Clinic.c.c.cal Spectrum and Predictors of Poor Outcome. *Clin. Infect. Dis.* **2022**, *74*, 604–613. [[CrossRef](#)] [[PubMed](#)]
127. McNeil, J.C.; Kok, E.Y.; Forbes, A.R.; Lamberth, L.; Hulten, K.G.; Vallejo, J.G.; Mason, E.O.; Kaplan, S.L. Healthcare-associated Staphylococcus aureus Bacteremia in Children: Evidence for Reverse Vancomycin Creep and Impact of Vancomycin Trough Values on Outcome. *Pediatr. Infect. Dis. J.* **2016**, *35*, 263–268. [[CrossRef](#)] [[PubMed](#)]
128. Rouzic, N.; Janvier, F.; Libert, N.; Javouhey, E.; Lina, G.; Nizou, J.Y.; Pasquier, P.; Stamm, D.; Brinquin, L.; Pelletier, C.; et al. Prompt and successful toxin-targeting treatment of three patients with necrotizing pneumonia due to Staphylococcus aureus strains carrying the Panton-Valentine leukocidin genes. *J. Clin. Microbiol.* **2010**, *48*, 1952–1955. [[CrossRef](#)]
129. Cardot-Martin, E.; Casalegno, J.S.; Badiou, C.; Dauwalder, O.; Keller, D.; Prevost, G.; Rieg, S.; Kern, W.V.; Cuerq, C.; Etienne, J.; et al. alpha-Defensins partially protect human neutrophils against Panton-Valentine leukocidin produced by Staphylococcus aureus. *Letts. Appl. Microbiol.* **2015**, *61*, 158–164. [[CrossRef](#)]
130. Tsai, T.A.; Tsai, C.K.; Kuo, K.C.; Yu, H.R. Rational stepwise approach for Mycoplasma pneumoniae pneumonia in children. *J. Microbiol. Immunol. Infect.* **2021**, *54*, 557–565. [[CrossRef](#)]
131. Shen, Y.; Zhang, J.; Hu, Y.; Shen, K. Combination therapy with immune-modulators and moxifloxacin on fulminant macrolide-resistant Mycoplasma pneumoniae infection: A case report. *Pediatr. Pulmonol.* **2013**, *48*, 519–522. [[CrossRef](#)] [[PubMed](#)]
132. Shopsin, B.; Kaveri, S.V.; Bayry, J. Tackling Difficult Staphylococcus aureus Infections: Antibodies Show the Way. *Cell Host Microbe* **2016**, *20*, 555–557. [[CrossRef](#)]
133. Zhang, Y.; Chen, Y.; Chen, Z.; Zhou, Y.; Sheng, Y.; Xu, D.; Wang, Y. Effects of bronchoalveolar lavage on refractory Mycoplasma pneumoniae pneumonia. *Respir Care* **2014**, *59*, 1433–1439. [[CrossRef](#)] [[PubMed](#)]
134. Kapur, N.; Slater, A.; McEniery, J.; Greer, M.L.; Masters, I.B.; Chang, A.B. Therapeutic bronchoscopy in a child with sand aspiration and respiratory failure from near drowning—Case report and literature review. *Pediatr. Pulmonol.* **2009**, *44*, 1043–1047. [[CrossRef](#)]
135. Sharp, J.K.; Hereth, J.; Fasanello, J. Bronchoscopic findings in a child with pandemic novel H1N1 influenza A and methicillin-resistant Staphylococcus aureus. *Pediatr. Pulmonol.* **2011**, *46*, 92–95. [[CrossRef](#)]
136. Dalponte, R.S.; Heluany, G.C.V.; Michels, M.; Madeira, K.; Prado, C.E. Surgical treatment of necrotizing pneumonia in children: A 10-year assessment. *Rev. Col. Bras. Cir.* **2020**, *47*, e20202374. [[CrossRef](#)] [[PubMed](#)]
137. Macedo, M.; Meyer, K.F.; Oliveira, T.C. Necrotizing pneumonia in children submitted to thoracoscopy due to pleural empyema: Incidence, treatment and clinical evolution. *J. Bras. Pneumol.* **2010**, *36*, 301–305. [[CrossRef](#)]
138. Chen, J.S.; Huang, K.C.; Chen, Y.C.; Hsu, H.H.; Kuo, S.W.; Huang, P.M.; Lee, J.M.; Lee, Y.C. Pediatric empyema: Outcome analysis of thoracoscopic management. *J. Thorac. Cardiovasc. Surg.* **2009**, *137*, 1195–1199. [[CrossRef](#)]
139. Ayed, A.K.; Al-Rowayeh, A. Lung resection in children for infectious pulmonary diseases. *Pediatr. Surg. Int.* **2005**, *21*, 604–608. [[CrossRef](#)]
140. Klouda, T.; Gunnlaugsson, S.; Shashi, K.; Alomari, A.; Fishman, M.P.; Casey, A. Nonsurgical management of dynamic pneumatocele via endobronchial administration of fibrin sealant. *Pediatr. Pulmonol.* **2021**, *56*, 3425–3428. [[CrossRef](#)]
141. Westphal, F.L.; Lima, L.C.; Netto, J.C.; Tavares, E.; Andrade Ede, O.; Silva Mdos, S. Surgical treatment of children with necrotizing pneumonia. *J. Bras. Pneumol.* **2010**, *36*, 716–723. [[CrossRef](#)] [[PubMed](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.