Systematic Review

Acute Pancreatitis Associated with Atypical Bacterial Pneumonia: Systematic Literature Review

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Abstract: Background: Extra-pulmonary features sometimes occur in association with atypical bacterial pneumonia and include neurologic manifestations, diarrhea, rashes, altered liver enzymes, or kidney injury, among other conditions. Acute pancreatitis has been associated with atypical pneumonias since 1973. Methods: We performed a systematic review of the literature in the Excerpta Medica, National Library of Medicine, and Web of Science databases. We retained 27 reports published between 1973 and 2022 describing subjects with an atypical pneumonia temporally associated with acute pancreatitis. Results: The reports included 33 subjects (19 males, and 14 females; 8 children and 25 adults) with acute pancreatitis temporally associated with atypical pneumonia caused by Mycoplasma pneumoniae (n = 18), Legionella species (n = 14), or Coxiella burnetii (n = 1). Approximately 90% of patients (n = 29) concurrently presented with respiratory and pancreatic diseases. No cases associated with Chlamydophila pneumoniae, Chlamydophila psittaci, or Francisella species were found. Conclusions: Acute pancreatitis has been associated with various infectious agents. The present review documents the association with atypical pneumonia induced by Mycoplasma pneumoniae, Legionella species, and Coxiella burnetii.

Keywords: atypical pneumonia; acute pancreatitis; Coxiella burnetii; Legionella species; Mycoplasma pneumoniae

1. Introduction

The term atypical bacterial pneumonia denotes pulmonary infections caused by Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Francisella species, and especially Legionella species and Mycoplasma pneumoniae [1,2]. These bacteria are responsible for 15–20% of community-acquired pneumonia cases [1,2].

Non-pulmonary features are common in patients affected by atypical bacterial pneumonia conditions [2–5]. The reported non-pulmonary features include abdominal pain, nausea or vomiting, ileus, diarrhea, jaundice, elevated aminotransferases, nervous system dysfunction (including headache, mental confusion, and reduced levels of consciousness), acute kidney injury, and skin rashes, among others. Interestingly, the non-pulmonary features of patients with an atypical bacterial pneumonia syndrome may
precede the respiratory disease, may present concomitantly with the respiratory disease, or after the respiratory disease [2–5].

Acute pancreatitis has been associated with atypical bacterial pneumonia since 1973 [6]. As this issue has never been systematically evaluated, we performed a systematic review of the literature. The study aimed to gain insight into the features of pancreatitis associated with atypical pneumonias and to speculate on the mechanisms underlying acute pancreatitis in these patients.

**2. Materials and Methods**

2.1. **Search Strategy**

We performed a structured literature search with no date or language restrictions in the databases Excerpta Medica, National Library of Medicine, and Web of Science, in accordance with the guidelines of the 2020 version of the Preferred Reporting of Systematic Reviews and Meta-Analyses [7]. Search terms were (“atypical pneumonia” OR “Chlamydia pneumoniae” OR “Chlamydia psittaci” OR “Chlamydophila pneumoniae” OR “Chlamydophila psittaci” OR “Coxiella burnetii” OR “Francisella tularensis” OR “Legionella” OR “Mycoplasma pneumoniae”) AND (“acute pancreatitis”). The bibliography of each identified report was also screened for secondary references. Additionally, to detect as many cases as possible, articles published in non-indexed journals were also evaluated. The search was carried out in April 2022 and was repeated before submission.

2.2. **Eligibility Criteria—Case Selection**

All original articles or letters reporting humans with a community-acquired pneumonia caused by *Chlamydia pneumoniae, Chlamydia psittaci, Coxiella burnetii, Francisella tularensis, Legionella species,* or *Mycoplasma pneumoniae* temporally associated with an acute pancreatitis were considered eligible. Inclusion was restricted to apparently immunocompetent subjects. The diagnosis of pneumonia caused by an atypical pathogen was only retained in cases with both a characteristic clinical presentation and appropriate microbiology laboratory testing [1,2]. A diagnosis of acute pancreatitis was made in patients with an increase in amylase or lipase values to >3 times the upper normal laboratory limit, irrespective of the clinical and imaging features [8]. The Institutional Review Board authorization was not a prerequisite for this systematic literature review. After an initial selection round based on the title and abstract, the eligibility of the full text of the selected reports was assessed. The gray literature was assessed in the same way.

2.3. **Data Extraction**

The following four groups of data were collected from each patient, using a predesigned data extraction form: (1) demographics, pre-existing conditions—with emphasis on recognized precipitants of acute pancreatitis (chronic alcohol use disorder, gallstones, hypercalcemia, increased triglyceride levels, and medication with drugs [9] implicated as a causative agent for acute pancreatitis), and microbiology laboratory testing; (2) the temporal relationship between respiratory disease and the onset of pancreatitis (the term pre-infectious denoted cases with pancreatitis preceding pneumonia by ≤10 days, the term intra-infectious denoted cases with concomitant presentation of pneumonia and pancreatitis, and the term post-infectious denoted cases with pneumonia preceding pancreatitis by ≤10 days), abdominal involvement (pain, nausea or vomiting, ileus, diarrhea, and jaundice), an increase in alanine or aspartate aminotransferase levels (more than twice the upper limit of normal), and imaging studies to categorize pancreatitis as interstitial edematous or necrotizing [9,10]; (3) non-pulmonary features including central nervous system dysfunction (headache, mental confusion, and reduced levels of consciousness), the occurrence of acute kidney injury
using the KDIGO criteria [11], the occurrence of multiple organ dysfunction [12], and skin rashes; (4) the length of hospitalization and the occurrence of death.

The literature search, the selection of reports retained for analysis, and the data extraction process were independently carried out by two authors in an unblinded fashion with the support of an experienced investigator. Two authors entered the data into a piloted database, and the experienced investigator verified the accuracy of the data entries.

2.4. Comprehensiveness of Reporting—Analysis

Each of the four groups of extracted data was rated for completeness [13] (0, 1, or 2) and the reporting quality was graded according to the sum (excellent ≥6), good (4–5), or acceptable (3–4)).

Pairwise deletion was used to deal with any missing data. The categorical data are shown as counts and were analyzed using Fisher’s exact test. The continuous data are presented as medians and interquartile ranges and were analyzed using the Mann–Whitney–Wilcoxon U test. Two-sided p values of <0.05 were considered to be significant.

3. Results

The literature search process is outlined in Figure 1.

![Figure 1](image-url)

Figure 1. Acute pancreatitis associated with atypical bacterial pneumonia. Flowchart of the literature search.

Six reports were excluded because lacking clinical signs and symptoms of pneumonia. Swedish patients reported twice in the literature [6,14] were considered only once. For the final analysis, we retained 27 reports [6,14–39] published between 1973 and 2022 from France (n = 7), the United States of America (n = 3), Belgium (n = 3), Sweden (n = 3), Spain (n = 2), Denmark (n = 1), the United Kingdom (n = 1), Germany (n = 1), Italy (n = 1), Japan (n = 1), India (n = 1), South Korea (n = 1), Switzerland (n = 1), and Venezuela (n = 1). Eighteen articles were written in English, four in French, three in Spanish, one in German, and one in Danish.

The reports included 33 subjects with pancreatitis temporally associated with an atypical pneumonia: 18 cases associated with *Mycoplasma pneumoniae* [6,14–26], 14 cases
associated with Legionella species [27–38], and 1 case associated with Coxiella burnetii [39]. The reports did not include any case of acute pancreatitis temporally associated with pneumonia caused by Chlamydia pneumoniae, Chlamydia psittaci, or Francisella species.

The completeness of reporting was excellent in 19 cases (Legionella, n = 11; Mycoplasma, n = 8), good in 8 cases (Mycoplasma, n = 5; Legionella, n = 3), and acceptable in the remaining 6 cases (Mycoplasma, n = 5; Coxiella, n = 1).

3.1. Microbiological Diagnosis

The microbiological diagnosis of Mycoplasma pneumoniae infection was made by detecting a significant rise in immunoglobulin G titer levels when comparing acute and convalescent blood samples (n = 17) or both an antibody titer and a positive Mycoplasma test in a respiratory tract sample (n = 1). The laboratory diagnosis of Legionella infection was made by means of a positive sputum or tissue testing (n = 6), a rise in immunoglobulin G titer levels (n = 5), or a positive urinary test (n = 3). The diagnosis of Coxiella infection was made by means of a rise in immunoglobulin G titer levels (n = 1).

3.2. Clinical and Laboratory Features

The characteristics of the 32 patients are presented in Table 1. Patients with atypical pneumonia and acute pancreatitis associated with Mycoplasma pneumoniae were more frequently male (p = 0.0116) and younger (p = 0.0112) than those with Legionella species infection. Approximately 90% of patients presented with concurrent respiratory and pancreatic disease. None of the 33 patients were affected by chronic alcohol use disorder, hypercalcemia, and hypertriglyceridemia, or underwent treatment with a drug potentially associated with acute pancreatitis. A 62-year-old man concurrently presented with an asymptomatic cholelithiasis [14].

Table 1. Characteristics of 33 patients (3 to 88 years of age with atypical bacterial pneumonia associated with acute pancreatitis). Data are presented as the frequency (with percentage) or median (with interquartile range).

<table>
<thead>
<tr>
<th></th>
<th>All Cases</th>
<th>Mycoplasma pneumoniae</th>
<th>Legionella Species</th>
<th>Coxiella burnetii</th>
<th>p-Values x</th>
</tr>
</thead>
<tbody>
<tr>
<td>n females:males, n</td>
<td>14:19</td>
<td>11:7</td>
<td>2:12</td>
<td>1:0</td>
<td>0.0116</td>
</tr>
<tr>
<td>age years, n (%), &lt;20 years</td>
<td>8 (24)</td>
<td>8 (47)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.0044</td>
</tr>
<tr>
<td>temporal relationship to pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-infectious, n (%)</td>
<td>1 (3.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0.9999</td>
</tr>
<tr>
<td>intra-infectious, n (%)</td>
<td>29 (88)</td>
<td>16 (89)</td>
<td>13 (93)</td>
<td>0 (0)</td>
<td>0.9999</td>
</tr>
<tr>
<td>post-infectious, n (%)</td>
<td>3 (9.1)</td>
<td>2 (11)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
<td>0.9999</td>
</tr>
<tr>
<td>abdominal features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abdominal pain, n (%)</td>
<td>25 (76)</td>
<td>16 (89)</td>
<td>9 (64)</td>
<td>0 (0)</td>
<td>0.1948</td>
</tr>
<tr>
<td>nausea, vomiting, n (%)</td>
<td>14 (44)</td>
<td>10 (56)</td>
<td>4 (29)</td>
<td>0 (0)</td>
<td>0.7249</td>
</tr>
<tr>
<td>ileus, n (%)</td>
<td>7 (21)</td>
<td>5 (28)</td>
<td>2 (14)</td>
<td>0 (0)</td>
<td>0.4264</td>
</tr>
</tbody>
</table>
The following abdominal features were observed: abdominal pain, nausea or vomiting, ileus, diarrhea, jaundice, and elevated aminotransferases. Diarrhea ($p = 0.0099$), jaundice ($p = 0.0278$), and elevated liver enzymes ($p = 0.0002$) were more commonly observed in cases caused by Legionella.

No pancreatic imaging studies were carried out in 12 cases. The following imaging studies were performed in the remaining patients: ultrasound and computed tomography ($n = 9$); ultrasound ($n = 8$); and computed tomography ($n = 4$). Edema was identified following imaging in 14 cases and necrosis in 5 cases, respectively.

The prevalence of central nervous system dysfunction ($p = 0.0002$) and acute kidney injury ($p = 0.0037$) was higher in Legionella cases than in Mycoplasma cases. A skin rash was rarely reported.

Multi-organ dysfunction occurred in seven cases. Two of them, a 68-year-old female reported in 1974 [14] and a 66-year-old man reported in 1986 [29], died.

4. Discussion

Acute pancreatitis mostly occurs in subjects with chronic alcohol use disorders, cholelithiasis or choledocholithiasis, hypercalcemia, and hypertriglyceridemia, or is drug-induced [8,9]. The present systematic review demonstrates that acute pancreatitis may be temporally associated with a community-acquired atypical pneumonia syndrome caused by Mycoplasma pneumoniae, Legionella species, or Coxiella burnetii (both in childhood and adulthood). In contrast, no cases associated with the remaining bacterial pathogens of atypical pneumonia were found.

The pathophysiology of acute pancreatitis associated with atypical pneumonia caused by Mycoplasma pneumoniae or Legionella species is elusive. Mycoplasma pneumoniae...
Acute pancreatitis has been associated with infectious agents such as mumps virus, coxsackieviruses, cytomegalovirus, hepatitis B virus, herpes simplex virus, severe acute respiratory syndrome coronavirus 2, varicella-zoster virus, aspergillus, ascaris, cryptosporidium, toxoplasma, leptospira, and salmonella [48,49]. The present review of the literature documents the association with *Mycoplasma pneumoniae, Legionella* species, and *Coxiella burnetii*. 

5. Conclusions

Acute pancreatitis has been associated with infectious agents such as mumps virus, coxsackieviruses, cytomegalovirus, hepatitis B virus, herpes simplex virus, severe acute respiratory syndrome coronavirus 2, varicella-zoster virus, aspergillus, ascaris, cryptosporidium, toxoplasma, leptospira, and salmonella [48,49]. The present review of the literature documents the association with *Mycoplasma pneumoniae, Legionella* species, and *Coxiella burnetii*. 

Immunoglobulin M antibodies against *Mycoplasma pneumoniae* are detected [45] in blood in approximately one-third of patients with acute pancreatitis (and some patients with acute meningoencephalitis). It has therefore been postulated that, during pancreatitis, antigenic sequences similar to the major antigens of *Mycoplasma pneumoniae* are revealed, which elicit an immunoglobulin M antibody response [45]. For this reason [46], only acute pancreatitis cases associated both with acute respiratory disease and an appropriate microbiology laboratory test were included in the present analysis (an immunoglobulin M detection was not accepted as a stand-alone diagnostic test).

The practical relevance of this literature review is three-fold. First, acute pancreatitis can be added to the list of possible causes of abdominal symptoms in patients with atypical bacterial pneumonia. Patients with pancreatitis typically complain of upper abdominal and back pain, often associated with nausea and vomiting. Second, the diagnosis of atypical pneumonia deserves consideration in pancreatitis cases without a precipitant (such as gallstones, alcohol use disorders, hypercalcemia, and hypertriglyceridemia) or without any medication implicated as causative for acute pancreatitis. Finally, pancreatitis adds to the already rather long list of non-pulmonary features associated with atypical bacterial pneumonia.

First-line treatment options which are currently recommended for *Mycoplasma* infections include the macrolide azithromycin, the tetracycline doxycycline (doxycycline is unlikely to cause tooth discoloration in young children, contrary to other tetracyclines), or a respiratory fluoroquinolone (i.e., levofloxacin or moxifloxacin) [1]. Azithromycin or levofloxacin are the preferred antimicrobials for *Legionella* infections [1]. Acute *Coxiella* infections are treated with doxycycline [1]. No cases of pancreatitis have been causally associated with azithromycin, doxycycline, levofloxacin, or moxifloxacin [9].

The results of this literature review must be viewed with an understanding of the inherent limitations of the analysis, which included data from less than 30 reports published over a period of approximately 50 years. The available information did not allow the severity of pancreatitis to be stratified using a recognized classification. Moreover, a temporal association between an atypical bacterial pneumonia and pancreatitis does not necessarily imply causality. The prevalence of pancreatitis complicating atypical bacterial pneumonia is currently unknown (but is likely low). Finally, the analysis did not address atypical pneumonias triggered by viral pathogens, including respiratory syncytial viruses, parainfluenza viruses, influenza viruses, paramyxoviruses, and adenoviruses, among others. Recent data suggest that severe acute respiratory syndrome coronavirus 2 may also be associated with acute pancreatitis [47].


### Author Contributions

Conceptualization, M.G.B. and S.J.; methodology, G.P.M.; formal analysis, M.G.B. and G.G.; investigation, G.G. and G.A.M.V.; data curation, L.K., S.A.G.L., P.B.F., and C.A.; significant intellectual contribution, all authors; writing—original draft preparation, M.G.B., S.J., and G.P.M.; writing—review and editing, all the authors; funding acquisition, S.A.G.L. and C.A. All authors have read and agreed to the published version of the manuscript.

### Funding

The study was partially founded by the Italian Ministry of Health (Current Research IRCCS).

### Institutional Review Board Statement

Not applicable.

### Informed Consent Statement

Not applicable.

### Data Availability Statement

Data are available upon reasonable request to the corresponding authors.

### Acknowledgments

The authors are particularly grateful to Craig Laurence for linguistic assistance. S.A.G.L. is the current recipient of research grants from Fonds de perfectionnement, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Fondation SICPA, Prilly, Switzerland; Fondazione Dr. Ettore Balli, Bellinzona, Switzerland; Fondazione per il bambino malato della Svizzera italiana, Bellinzona, Switzerland; and Frieda Locher-Hofmann Stiftung, Zürich, Switzerland.

### Conflicts of Interest

The authors declare no conflicts of interest.

### References


