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ORIGINAL RESEARCH

Severe *Salmonella* Infections in AIGAs Immunodeficiency Syndrome: Hyperinflammation and Immune Dysregulation

Siqiao Liang[1,*], Fushou Chen[2,*], Xuemei Huang[1], Yan Ning[1], Siyao Wu[1], Limei Hong[1], Ni Chen[1], Hanlin Liang[1], Mengchan Wang[1], Xiaona Liang[1], Zhiyi He[1]

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, Wuming Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhiyi He; Xiaona Liang, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuang Yong Road, Nanning, Guangxi, 530021, People's Republic of China, Email zhiyi-river@163.com; xnliang0318@163.com

Background: Anti-interferon-γ autoantibodies (AIGAs) immunodeficiency syndrome is a rare acquired disorder characterized by impaired IFN-γ signaling, predisposing patients to severe intracellular infections. While disseminated *non-tuberculous mycobacteria* (NTM) and *Talaromyces marneffei* (TM) are well-documented pathogens, the clinical and immunological features of *Salmonella* coinfection remain poorly characterized.

Methods: This retrospective study analyzed 12 HIV-negative patients with AIGAs-positive status and confirmed *Salmonella* infection at the First Affiliated Hospital of Guangxi Medical University, China (2021–2024). Data included demographics, clinical manifestations, laboratory findings, co-infections, treatment, and outcomes. AIGAs were detected via ELISA and Western blot, with neutralizing activity confirmed by STAT1 phosphorylation inhibition.

Results: The cohort was predominantly composed of middle-aged males (83.3%, mean age 55.75 ±8.06 years). The most common symptoms were fever, fatigue and cough (each 91.7%), followed by poor appetite (83.3%), systemic symptoms (chills, weight loss; 58.3%) and dyspnea (58.3%). Bone or joint pain occurred in 41.7% and gastrointestinal complaints (abdominal pain, diarrhea or distension) in 25%. Five patients (41.7%) developed septic shock, three requiring vasopressors and two mechanical ventilations. All had high AIGAs titres (1:2500) and hyper-inflammation (median WBC17.3×10^9/L, CRP138.1mg/dL, PCT1.28ng/mL). Bacteraemia was present in 91.7% and mortality was 16.7% (2/12). Polymicrobial co-infection was universal; notably cytomegalovirus (50%) and TM (25%). Immunological profiling showed hyperglobulinaemia (IgG23.5±10.6g/L) and elevated IgE (257.5[79.7–598.2]IU/mL). Despite broad-spectrum antibiotics (83.3% survival), both fatalities occurred in patients who had not undergone NGS-based diagnosis.

Conclusion: This study is the first to define AIGAs-associated *Salmonella* infection as a distinct clinical syndrome, characterized by severe bacteremia, paradoxical hyperinflammation, universal polymicrobial coinfections, and immune dysregulation. Our findings underscore the critical importance of comprehensive pathogen detection, particularly via NGS, for timely diagnosis and improved patient outcomes.

Keywords: anti-interferon-γ autoantibodies, *Salmonella*, hyperinflammation, opportunistic infections, immunodeficiency

Introduction

Anti-interferon-γ autoantibodies (AIGAs) immunodeficiency syndrome, first identified in 2004 in patients with disseminated *non-tuberculous mycobacteria* (NTM) infections,[1] is a rare acquired immunodeficiency disorder. The disease is characterized by high-titer neutralizing AIGAs that bind to IFN-γ, blocking its interaction with the receptor and inhibiting downstream JAK1/STAT1 signaling.[2,3] Normally, IFN-γ activates macrophages and stimulates IL-12 production to clear intracellular pathogens.[4] However, AIGAs inhibit this process by preventing STAT-1 phosphorylation and disrupting

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downstream signaling. Consequently, the antimicrobial immune response mediated by monocytes and macrophages is severely compromised, significantly reducing the host's ability to eliminate intracellular pathogens.

AIGAs immunodeficiency syndrome exhibits distinct regional prevalence, with higher incidence rates in Southeast Asia and southern China, including Guangxi Province.[5,6] Our previous cohort studies have documented cases across all 14 regions of Guangxi.[6]

Clinically, AIGAs immunodeficiency syndrome primarily manifests as recurrent disseminated opportunistic infections, with NTM and *Talaromyces marneffei* (TM) being the most frequently reported pathogens.[5,6] Notably, *Salmonella*, a facultative intracellular bacterium, often causes severe, recurrent, and refractory infections in these patients. Due to impaired IFN-γ signaling, the host's ability to clear *Salmonella* is markedly diminished, leading to persistent fever, recurrent bacteremia, and multi-system involvement, with poor responses to conventional antimicrobial therapy.[7,8]

Currently, systematic studies on the clinical characteristics and therapeutic strategies for AIGAs immunodeficiency syndrome complicated by *Salmonella* infection remain limited. This report is the first dedicated cohort analysis to integrate longitudinal clinical data, comprehensive immunological profiling, and next-generation sequencing (NGS)-based pathogen detection in *Salmonella*-AIGAs immunodeficiency syndrome cases. By retrospectively analyzing 12 consecutive patients from Guangxi, we quantify the true burden of *Salmonella* disease in this setting, define hyper-inflammatory biomarker signatures, and evaluate the impact of NGS-guided precision therapy on survival. These data directly address the existing knowledge gap by providing evidence-based algorithms for early recognition, optimal antimicrobial combinations, and timely introduction of targeted immunomodulation, thereby improving outcomes beyond the historical experience confined to case reports or small mixed-pathogen series.

Materials and Methods

Study Population

This study retrospectively collected data from 12 HIV-negative patients with AIGAs immunodeficiency syndrome complicated by *Salmonella* infection admitted to the First Affiliated Hospital of Guangxi Medical University from January 2021 to December 2024. The data included demographics, clinical manifestations, laboratory tests, imaging studies, pathological examinations, treatment processes, and outcomes.

Diagnosis of AIGAs Immunodeficiency Syndrome

The diagnosis of AIGAs immunodeficiency syndrome was based on clinical manifestations and laboratory tests. The core criteria include: (1) susceptibility to opportunistic infections, particularly intracellular pathogens such as NTM, TM, and *Salmonella*; (2) positive detection of AIGAs in serum by indirect ELISA, with neutralizing capacity confirmed by Western blot (WB).

AIGAs Assays

1ELISA for Qualitative Detection of AIGAs

Recombinant human IFN-γ (2 μg/mL) was used to coat 96-well plates, which were incubated at 4°C for 12 hours. After blocking, diluted test sera (1:100, 1:500, 1:2500) were added and incubated at room temperature for 2 hours. HRP-conjugated secondary antibody was then added, followed by TMB substrate. OD values at 450 nm were measured, with OD $\geq$ 0.5 considered positive.

2WB for Verification of AIGAs Neutralizing Activity by Western Blot

THP-1 cells, obtained from the Chinese Academy of Sciences Stem Cell Bank (catalogue No. SCSP-567), were differentiated into macrophages with PMA and then co-cultured with IFN-γ-pre-incubated serum for 12 h. The cells were then lysed, and the proteins were separated by SDS-PAGE and transferred to a membrane for blotting. The expression of p-STAT1 was detected. In AIGAs-positive samples, p-STAT1 expression was reduced or absent due to IFN-γ neutralization, whereas control samples showed normal expression.

Diagnostic Criteria for Salmonella Infection

The diagnosis of *Salmonella* infection is based on a combination of microbiological, clinical, and epidemiological data. The main criteria include: (1) positive culture of *Salmonella* spp. from sterile sites (eg, blood, bone marrow) or non-sterile sites (eg, stool, urine); (2) detection of *Salmonella*-specific sequences by next-generation sequencing (NGS) in clinical samples. Meeting either criterion confirms *Salmonella* infection.

Diagnostic Criteria for Other Pathogen Infections

NTM Infection: Diagnosis followed the "Guidelines for the Diagnosis and Treatment of NTM Disease".[9]

TM Infection: Diagnosis was confirmed by: (a) detection of TM-specific sequences in qualified clinical samples (eg, bronchoalveolar lavage fluid, lymph node aspirate, purulent exudate, blood, or sputum) by NGS; (b) isolation of TM from clinical samples cultured at 25°C or 37°C; (c) histopathological identification of characteristic TM fungal spores. Meeting any of these criteria confirmed TM infection.

Other Pathogens: NGS, microbial culture, and histopathological results were also applicable for diagnosing infections caused by other pathogens, including viruses, *Burkholderia, Staphylococcus aureus, Klebsiella pneumoniae*, and various fungi.

Efficacy Evaluation Criteria

Improvement: Significant clinical symptom improvement, decreased pathogen detection, and radiological evidence of lesion reduction after anti-infection therapy.

Failure: No improvement or worsening of clinical symptoms, persistent positive pathogen detection, and no change or progression of lesions on imaging after standardized anti-infection therapy.

Death: Death directly attributed to *Salmonella* infection during treatment.

Statistical Analysis

Continuous variables are presented as mean±standard deviation (X±S). For normally distributed data (Shapiro–Wilk test) with homogeneous variances (Levene test), intergroup comparisons were performed using independent sample *t*-tests; otherwise, the Mann–Whitney *U*-test was used. Categorical variables are presented as counts (percentages), with intergroup comparisons using χ^2-tests or Fisher's exact test (when expected frequencies <5). All statistical analyses were conducted using SPSS (version 27.0), with $P<0.05$ indicating statistical significance.

Results

Demographic Characteristics

A total of 12 patients were enrolled in this study, including 10 males (83.3%) and 2 females (16.7%). The age at onset ranged from 44 to 70 years, with a mean age of 55.75±8.06 years (Table 1). All participants were residents of Guangxi Province of China, comprising 5 Zhuang ethnic patients (41.7%) and 7 Han ethnic patients (58.3%). Regarding occupational distribution, 7 cases (58.3%) were farmers, 2 (16.7%) were self-employed individuals, and the remaining 3 (25.0%) had other occupations.

Analysis of Underlying Comorbidities

Among the 12 enrolled patients, 5 (41.7%) had pre-existing comorbidities. The specific conditions were distributed as follows: Case 1 had hypertension; Case 5 presented with diabetes mellitus, hypertension, and malignant tumor concurrently; Case 9 was diagnosed with cerebral infarction; Case 10 had a neurological disorder; and Case 11 suffered from chronic obstructive pulmonary disease (COPD). Detailed information is presented in Table 1.

Clinical Manifestations

In our cohort of 12 AIGAs-positive patients with *Salmonella* coinfection, fever, fatigue, and cough were most common (91.7% each), followed by poor appetite (83.3%) and sputum production (75%). Systemic symptoms (chills, weight loss) and dyspnea occurred in 58.3%. Musculoskeletal involvement included bone/joint pain (41.7%) and low back pain

Table 1 Demographic Characteristics, Symptoms and Signs in 12 Patients with AIGAs Immunodeficiency Syndrome and *Salmonella* Coinfection

Case	Gender	Age (Years)	Ethnicity	Comorbidities	Symptoms	Peak Temp (°C)	Signs	Shock	Vasopressor Use
1	Male	63	Han	Hypertension	Fever, fatigue, poor appetite, chills, cough, sputum, dyspnea, chest tightness	40.6	Pleural effusion signs	No	No
2	Male	49	Zhuang	–	Fever, fatigue, poor appetite, weight loss, cough, sputum, abdominal pain, diarrhea, abdominal distension	39.5	Jaundice of skin and sclera, anemic facies, moist rales, hepatomegaly, splenomegaly, abdominal muscle guarding, abdominal tenderness, rebound tenderness, lower limb edema	Yes	No
3	Female	46	Han	–	Fatigue, poor appetite, dyspnea, chest tightness, palpitations, somnolence	–	Rash, jaundice of skin and sclera, hepatomegaly, splenomegaly, neurological signs	Yes	Yes
4	Male	54	Han	–	Fever, fatigue, poor appetite, weight loss, chills/rigors, cough, sputum, hemoptysis, dyspnea, bone or joint pain, low back pain	38.9	Rash, cutaneous abscess, moist rales, hepatomegaly	No	No
5	Male	60	Han	Diabetes, hypertension, malignancy history	Fever, chills, cough, sputum	37.6	–	No	No
6	Male	70	Zhuang	–	Fever, fatigue, chills, cough, sputum, dyspnea, chest tightness, somnolence	38.6	Moist rales, dry rales	Yes	Yes
7	Male	46	Zhuang	–	Fever, fatigue, poor appetite, weight loss, cough, dyspnea, bone or joint pain, low back pain, dizziness/headache, limb numbness	39	Cutaneous abscess, anemic facies, hepatomegaly, splenomegaly	Yes	Yes
8	Male	44	Zhuang	–	Fever, fatigue, poor appetite, weight loss, chills, cough, abdominal pain, diarrhea, abdominal distension, vomiting, bone or joint pain, low back pain, somnolence	39.9	Anemic facies, moist rales, hepatomegaly, splenomegaly, neurological signs	Yes	No
9	Male	60	Han	History of cerebral infarction	Fever, fatigue, poor appetite, weight loss, chills, cough, sputum, dyspnea, limb numbness	39	Hepatomegaly, splenomegaly	No	No
10	Male	61	Zhuang	COPD	Fever, fatigue, poor appetite, cough, sputum, dyspnea, chest tightness, bone or joint pain	38.1	Rash	No	No
11	Female	56	Han	–	Fever, fatigue, poor appetite, weight loss, cough, sputum, diarrhea, nausea, vomiting, palpitations	38.3	Rash, anemic facies, moist rales, signs of lung consolidation	No	No
12	Male	60	Han	–	Fever, fatigue, poor appetite, weight loss, chills, cough, sputum, abdominal pain, abdominal distension, nausea, bone or joint pain, dizziness/headache, limb numbness	38.8	Anemic facies, moist rales, signs of lung consolidation	No	No

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(25%); gastrointestinal symptoms (abdominal pain, diarrhea, distension) were present in 25% each. Neurological manifestations included limb numbness/somnolence (25%) and dizziness/headache (16.7%); cardiorespiratory symptoms included chest tightness (33.3%) and palpitations (16.7%) (Figure 1).

On examination, moist rales and hepatomegaly were noted in 50% each, with anemic facies and splenomegaly in 41.7% each. Skin findings included rash (33.3%) and abscesses (16.7%). Pulmonary signs comprised consolidation (16.7%), dry rales (8.3%), and pleural effusion (8.3%). Neurological signs were observed in 16.7%; abdominal signs (guarding, tenderness, rebound) and edema were less common (8.3% each) (Figure 2).

Notably, five patients developed hypotension and septic shock; three required vasopressors. Two were admitted to the ICU and underwent intubation and mechanical ventilation (Table 1).

Diagnostic Methods for Salmonella Infection

Among the 12 AIGAs-positive patients with *Salmonella* infection, blood culture was the primary diagnostic method, yielding positive results in 10 cases (83.3%) (Supplementary Table 1). One patient (8.3%) was diagnosed via blood NGS alone, while four patients (33.3%) via NGS testing alongside blood cultures for confirmation. One patient (8.3%) was diagnosed through pus culture from a left-hand skin abscess, and one patient (8.3%) underwent combined blood and bone marrow cultures.

Laboratory Findings in Patients with AIGAs-Positive Salmonella Infection

All 12 patients had AIGAs 1:2500. Labs showed leukocytosis (median WBC17.35×10^9/L, IQR 11.23–20.59), neutrophilia (median N 14.18×10^9/L, IQR 8.64–18.49), anemia (mean Hb 97.60±24.99 g/L), and marked inflammation: CRP138.12±52.71 mg/dL, ESR53.00[22.25–109.75] mm/h, PCT 1.28[0.34–23.38] ng/mL, Serum ferritin 690.25 [-463.63–2012.79]ng/mL (Table 2).

Hyperimmunoglobulin (IgG 23.54±10.59 g/L) with elevated IgG4 (2.12 [1.47–5.97] g/L) and IgE (257.45[79.68–-598.20]IU/mL) was noted. Hepatic involvement manifested as hypoalbuminemia (27.19±5.08g/L), and decreased cholinesterase (3403.00 [2545.75–4021.25] U/L). Coagulation studies revealed prolonged PT (15.16 ± 3.67 s) and elevated D-dimer (877.50 [421.25–1537.25] ng/mL).

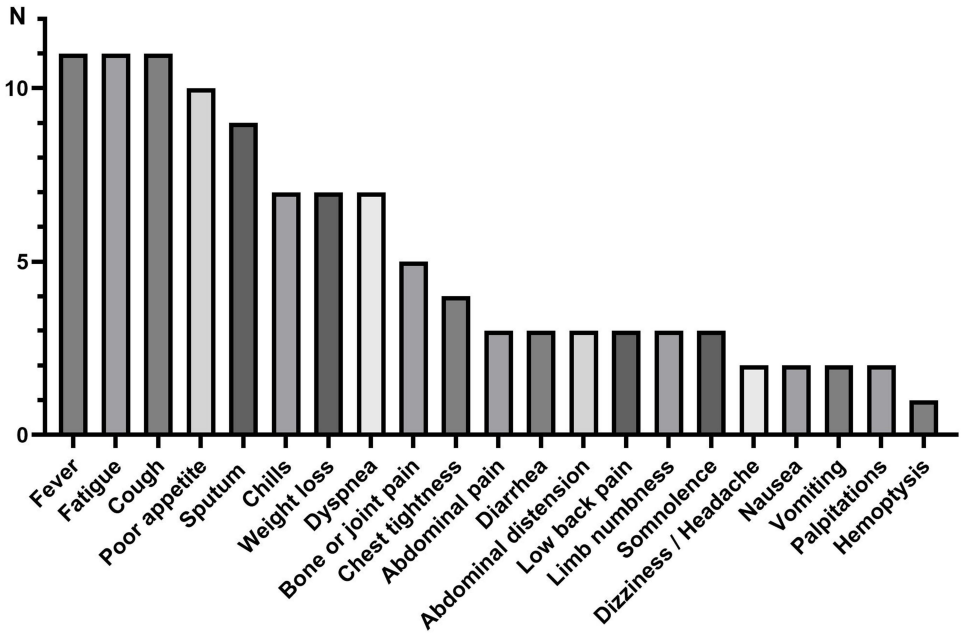

Figure 1 Distribution of clinical symptoms in 12 patients with AIGAs immunodeficiency syndrome and *Salmonella* coinfection.

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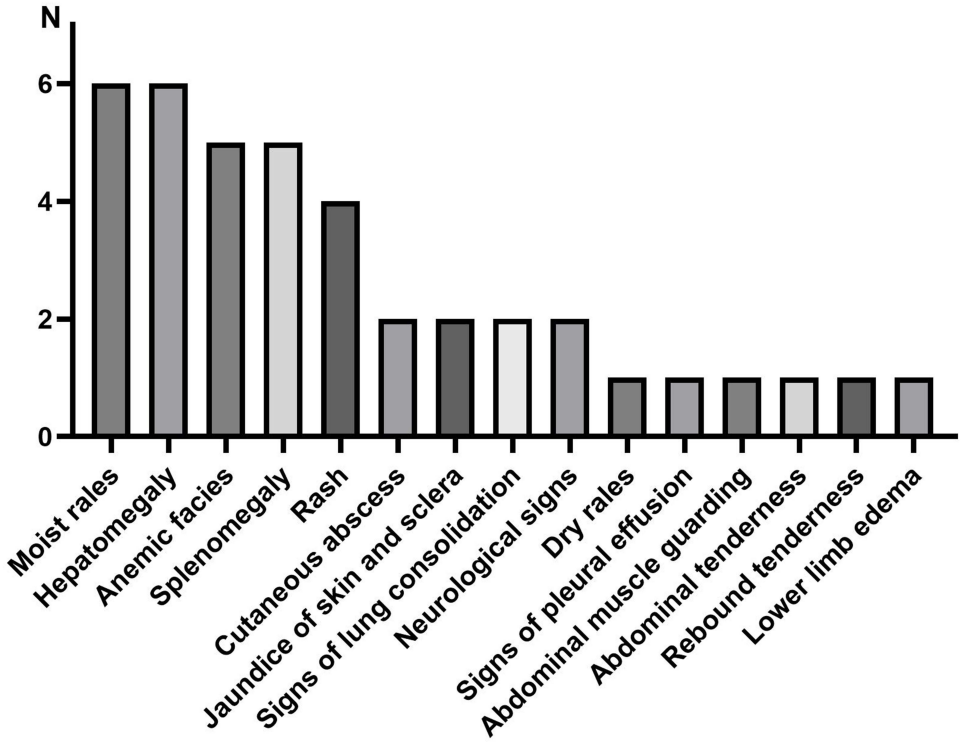

Figure 2 Distribution of clinical signs 12 patients with AIGAs immunodeficiency syndrome and *Salmonella* coinfection.

Further analysis of individual cases showed marked hematologic disturbance (Supplementary Table 2): Hb 59–146 g/L, with 5 (41.7%) <90 g/L; WBC 8.24–52.67×10^9/L, 2 (16.7%) >30×10^9/L; neutrophilia in 10 (83.3%), lymphopenia in 4 (33.3%); thrombocytopenia in 3 (25%) and thrombocytosis in 5 (41.7%).

Table 2 Analysis Results of Laboratory Data in 12 Patients with AIGAs Immunodeficiency Syndrome and *Salmonella* Coinfection

Variables	Mean±SD/IQR	Reference Range
Red Blood Cells, x10^9/L	4.00±0.76	4.3–5.8
Hemoglobin, g/L	97.60±24.99	115-150
White Blood Cells, x10^9/L	17.35[11.23–20.59]	3.50–9.50
Neutrophils, x10^9/L	14.18[8.64–18.49]	1.50–6.30
Lymphocytes, x10^9/L	1.54[0.83–2.48]	1.10–3.20
Eosinophils, x10^9/L	0.12[0.06–0.26]	0.02–0.52
Monocytes, x10^9/L	0.54±0.29	0.10-0.0.60
Platelet, x10^9/L	269.00[94.50–427.43]	125.00–350.00
Total T Lymphocytes, %	34.30±7.95	30.00–46.00
$CD4^+$T Lymphocytes, %	28.48±8.29	19.20–33.60
$CD8^+$T Lymphocytes, %	65.57±14.00	62.60–76.80
Natural Killer Cells, %	18.02±6.87	9.50–23.50
B Lymphocytes, %	9.71[7.08–15.77]	8.50–14.50
Immunoglobulin G, g/L	23.54±10.59	8.60–17.40
Immunoglobulin M, g/L	1.45±0.68	0.50–2.80
Immunoglobulin A, g/L	2.44±0.64	1.00–4.20
Immunoglobulin E, IU/mL	257.45[79.68–598.20]	<100.00
Immunoglobulin G4, g/L	2.12[1.47–5.97]	0-2.00

(*Continued*)

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Table 2 (Continued).

Variables	Mean±SD/IQR	Reference Range
Globulin, g/L	43.77±10.60	20.00–40.00
Albumin, g/L	27.19±5.08	40.00–55.00
C-reactive protein, mg/dl	138.12±52.71	<10.00
Erythrocyte sedimentation rate, mm/h	53.00[22.25–109.75]	0-20.00
Serum ferritin, ng/mL	690.25[463.63–2012.79]	21.8–274.66
Procalcitonin, ng/mL	1.28[0.34–23.38]	<0.05
Alanine aminotransferase, U/L	24.50[8.75–50.50]	7.00–40.00
Aspartate aminotransferase, U/L	27.50[12.25–76.75]	13.00–35.00
Total bilirubin, μmol/L	17.90[10.10–30.35]	0-21.00
Cholinesterase, U/L	3403.00[2545.75–4021.25]	5000.00–12,000.00
Urea, mmol/L	5.65[3.13–15.15]	2.60–7.50
Creatinine, μmol/L	74.00[51.50–243.75]	41.00–73.00
Na, mmol/L	136.56±4.37	137.00–147.00
K, mmol/L	3.69±0.67	3.50–5.30
CL, mmol/L	100.53±4.98	99.00–110.00
PT, s	15.16±3.67	9.00–15.00
APTT, s	33.09±3.83	23.00–40.00
PTA, %	67.83±17.68	70.00–130.00
FIB, g/L	4.60±1.58	2.00–5.00
D-dimer, ng/mL	877.50[421.25–1537.25]	0-450.00
PH	7.39±0.13	7.35–7.45
P_aCO2, mm/Hg	34.68±6.12	35.00–45.00
P_aO2, mm/Hg	81.54±14.63	83.00–108.00
P_aO_2/FiO_2	318.50±86.31	400.00–500.00

Notes: Reference ranges were established by the Clinical Laboratory of the First Affiliated Hospital of Guangxi Medical University (ISO15189 certified).

Inflammatory and immunological profiles revealed marked abnormalities. CRP levels were elevated in all cases (range 55.7–200 mg/L), with 5 cases (41.7%) exceeding 150 mg/L. Serum ferritin reached 20821 ng/mL in one patient. All patients showed elevated PCT levels (>0.05 ng/mL), with 4 cases (33.3%) demonstrating significantly increased PCT (>10 ng/mL; range 10.4–100 ng/mL).

Hyperimmunoglobulin (IgG range 18.75–40.69g/L) was present in 7 cases (58.3%), with IgG4 elevation (>2 g/L) in 7 patients (58.3%) and IgE elevation (>100 IU/mL) in 8 patients (66.7%). $CD4^+$T lymphopenia was seen in 4 cases (33.3%). Hepatic dysfunction was evident by hypoalbuminemia (range 20.6–38 g/L) in all cases and severe cholinesterase deficiency (<5000 U/L) in 11 cases (91.7%). Coagulation abnormalities included elevated D-dimer (range 217–4066 ng/mL) and prolonged PT (>15 s) in 4 cases (33.3%).

Co-Infecting Pathogens

Co-infection patterns were systematically analyzed in 12 AIGAs-positive patients with *Salmonella* infection (Supplementary Table 3). All cases showed polymicrobial co-infections alongside *Salmonella*. Fungal co-infections were prominent, with TM identified in 3 patients (25.0%), constituting the most frequent fungal pathogen. Bacterial co-infections exhibited considerable diversity, featuring *Pseudomonas aeruginosa* (2 cases), *Streptococcus pneumoniae* (2 cases), and *Acinetobacter baumannii* (1 case).

Viral co-infections were universally present, with human cytomegalovirus (CMV) detected in 6 patients (50.0%). Other herpesviruses were also prevalent, including Epstein-Barr virus (EBV; 2 cases) and human herpesvirus 1 (HHV-1; 2 cases). Case 10 displayed the most extensive co-infection profile, with 10 distinct pathogens encompassing *Mycobacterium avium-intracellulare*, *Orientia tsutsugamushi*, and multiple viral agents.

Table 3 Treatment Regimens and Outcomes in 12 Patients with AIGAs Immunodeficiency Syndrome and *Salmonella* Coinfection

Case	Pathogens Identified	Antibacterial/NTM Therapy	Antifungal Therapy	Outcome
1	*Talaromyces marneffei*, *Parvimonas micra*, Human cytomegalovirus (CMV), Torque teno virus (TTV)	Ceftazidime, Levofloxacin, Amikacin, Etimicin	Voriconazole	Improved
2	*Acinetobacter baumannii*, *Candida albicans*, Human cytomegalovirus (CMV), Human herpesvirus 1 (HHV-1)	Cefoperazone-Sulbactam, Polymyxin B, Levofloxacin, Tigecycline, Omadacycline, Ceftazidime-Avibactam, Amikacin, Vancomycin, Imipenem-Cilastatin, Piperacillin-Tazobactam	Voriconazole, Caspofungin	Improved
3	NGS not performed	Imipenem-Cilastatin	Amphotericin B	Death
4	*Talaromyces marneffei*, *Streptococcus pneumoniae*, *Haemophilus parainfluenzae*	Cefoperazone-Sulbactam, Amikacin	Amphotericin B	Improved
5	*Talaromyces marneffei*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, Human herpesvirus 1 (HHV-1), Human herpesvirus 4 (HHV-4/EBV), Human cytomegalovirus (CMV), Adenovirus, Epstein-Barr virus (EBV)	Levofloxacin	Voriconazole	Improved
6	NGS not performed	Cefoperazone-Sulbactam, Levofloxacin, Tigecycline, Imipenem-Cilastatin, Linezolid, Moxifloxacin	Amphotericin B	Death
7	*Escherichia coli*, *Aspergillus terreus*	Imipenem-Cilastatin, Azithromycin, Amikacin	Voriconazole, Amphotericin B	Improved
8	Human cytomegalovirus (CMV), *Cryptococcus spp.*	Omadacycline, Levofloxacin, Linezolid, Imipenem-Cilastatin	Amphotericin B, Voriconazole	Improved
9	NGS not performed	Ceftazidime, Levofloxacin, Imipenem-Cilastatin	Voriconazole	Improved
10	*Mycobacterium avium-intracellulare*, *Orientia tsutsugamushi*, *Pseudomonas aeruginosa*, *Enterobacter cloacae complex*, *Klebsiella variicola*, *Aspergillus lentulus*, Epstein-Barr virus (EBV), JC polyomavirus (JCV), Human cytomegalovirus (CMV), Human herpesvirus 6B (HHV-6B)	Moxifloxacin, Azithromycin, Etimicin, Omadacycline, Doxycycline, Levofloxacin, Linezolid, Imipenem-Cilastatin	-	Improved
11	NGS not performed	Amikacin, Moxifloxacin, Azithromycin, Linezolid, Ethambutol, Meropenem, Rifampin	-	Improved
12	*Stenotrophomonas maltophilia*, Human cytomegalovirus (CMV)	Omadacycline	Amphotericin B	Improved

Temporal analysis revealed that TM infection preceded *Salmonella* detection in 7 cases (58.3%), with a median interval of 5 months (range 3–21). One patient subsequently developed NTM infection during follow-up. Comprehensive pathogen characterization was limited in 3 cases (25%) due to unperformed NGS testing.

Treatment and Outcomes

Among 12 patients with AIGAs-positive *Salmonella* infections, 10 (83.3%) showed clinical improvement with combination therapy, while 2 (16.7%) required ICU admission with endotracheal intubation and mechanical ventilation but ultimately died (Table 3). All three cases with TM coinfection responded well to voriconazole or amphotericin B therapy. Notably, both fatal cases occurred in patients without NGS testing. The treatment regimens primarily consisted of β-lactams (cefoperazone-sulbactam or piperacillin-tazobactam), carbapenems (7 cases), and fluoroquinolones (8 cases). More complex co-infections required intensive regimens, with one patient receiving 10 antibiotics plus dual antifungals and another requiring 8 agents for mixed NTM, bacterial and fungal pathogens.

Discussion

This study provides the first comprehensive characterization of *Salmonella* infections in patients with AIGAs immunodeficiency syndrome, revealing distinct clinical and immunological patterns that differentiate this condition from other opportunistic infections. Our findings show that these patients present with severe systemic manifestations, including high rates of bacteremia (83.3%), marked inflammatory responses, and frequent polymicrobial co-infections. The near-universal presence of respiratory symptoms and hepatosplenomegaly reflects the tropism of intracellular pathogens in the setting of impaired IFN-γ signaling, while laboratory findings of hyperglobulinemia and elevated IgE suggest complex immune dysregulation beyond simple macrophage dysfunction.

The study primarily involved middle-aged and elderly male patients (83.3%), with a mean age of 55.75 years, most of whom were farmers (58.3%). These findings are consistent with previous reports on adult-onset immunodeficiency syndrome associated with AIGAs,[6,10] suggesting potential links to chronic environmental or occupational exposures.

Four patients had comorbidities such as hypertension and diabetes, which may exacerbate immunodeficiency and increase susceptibility to opportunistic infections. However, the interaction between metabolic disorders and AIGAs requires further investigation.

Salmonella infection typically initiates with intestinal epithelial invasion, circumventing gastric acid defenses and inducing local inflammation that manifests as non-typhoidal salmonellosis (NTS) with characteristic diarrhea and mucosal damage.[11] However, in the unique immunological milieu of immunodeficiency, this pathogen demonstrates enhanced virulence, frequently progressing to invasive disease (iNTS) with bacteremia and systemic inflammatory responses.[12,13] Our cohort of AIGAs-positive patients exhibited particularly severe manifestations, with 91.7% developing bacteremia and 41.7% progressing to septic shock-clinical outcomes that markedly exceed typical NTS presentations and underscore the critical role of intact IFN-γ signaling in *Salmonella* containment.

The observed disease severity reflects both the infectious process and underlying immune dysregulation. Patients demonstrated significantly profound inflammatory activation, consistent with previous reports of AIGAs immunodeficiency syndrome associated with other infections such as TM, NTM, and Mycobacterium tuberculosis.[14–18] Notably, 11 of the 12 patients in this study had bacteremia, manifesting as significantly elevated white blood cells, neutrophils, C-reactive protein, and procalcitonin, alongside characteristic immunological disturbances including hyperglobulinemia (IgG 23.54 ± 10.59 g/L) and paradoxical IgE elevation (257.45 IU/mL). These findings suggest that AIGAs-mediated IFN-γ blockade not only impairs pathogen clearance but also disrupts broader immune homeostasis, potentially through altered Th1/Th2 balance. This immune dysregulation was further evidenced by frequent co-infections with intracellular pathogens, particularly TM (25%) and CMV (50%), which share dependence on IFN-γ-mediated defenses.

Immunoglobulins are serum proteins that play crucial roles in immune function, with five main classes: IgG, IgM, IgA, IgD, and IgE. AIGAs, produced by B cells, predominantly consist of IgG1 and IgG4 subtypes, though multiple subtypes may coexist.[2,19] Previous studies have identified IgE-subtype autoantibodies in various diseases,[20] suggesting the need to investigate potential IgE-subtype AIGAs. In AIGAs-positive patients, elevated IgG and IgE levels indicate B-cell hyperactivity and ongoing humoral immune responses. While IgE elevation typically associates with allergies, autoimmune diseases, and immunodeficiencies,[21–23] none of our acutely infected study patients with high AIGAs titers showed allergic manifestations. This suggests their elevated IgE may be infection- or autoimmunity-related rather than allergy-mediated. These immunological alterations appear directly correlated with AIGAs-induced immune dysregulation.

This study highlights diagnostic limitations of blood cultures in detecting co-infections. The two fatal cases lacking NGS testing emphasize the need for comprehensive microbial detection. All patients showed high AIGAs titers (1:2500), confirming IFN-γ neutralization's central role and suggesting titer monitoring's potential for risk stratification. Clinically, AIGAs immunodeficiency predisposes to polymicrobial infections, particularly with high titers, necessitating multi-site sampling and advanced detection methods.

Current guidelines recommend 7–14 days of antibiotic therapy for *Salmonella* bacteremia, though immunocompromised patients typically necessitate extended courses (2–6 weeks).[24] In our cohort, patients received prolonged, pathogen-targeted regimens (eg, piperacillin-tazobactam or imipenem-cilastatin for bacterial infections; amphotericin B for TM). For uncomplicated *Salmonella* infections, first-line antimicrobial options include fluoroquinolones, third-generation cephalosporins, aminoglycosides, and tetracyclines. However, in patients with AIGAs immunodeficiency syndrome-a condition predisposing to polymicrobial infections-initial empirical therapy should provide broad-spectrum coverage against common opportunistic pathogens (particularly TM, NTM, and *Salmonella* species), especially in severe cases pending microbiological confirmation.

For AIGAs management, immunomodulators (eg, corticosteroids or rituximab) may reduce autoantibody titers, though evidence remains limited. Our prior work categorized stable-phase AIGAs into three subtypes based on autoantibody titers and immune activity.[6] Even post-infection, persistent hyperglobulinemia and elevated inflammatory markers suggest ongoing immune dysregulation, which low-dose steroids may partially ameliorate.

Limitations and Future Perspectives

Our study has several limitations: it is a single-centre, retrospective analysis with a small sample (n=12), entailing potential selection bias; serial AIGAs-titer monitoring was incomplete; and structured long-term follow-up was lacking,

all of which constrain generalisability. Future work should therefore establish a multicentre prospective registry that consecutively enrols patients, performs scheduled AIGAs-titer measurements, and tracks long-term outcomes to validate and extend these findings.

Conclusion

This study establishes AIGAs-associated *Salmonella* infection as a distinct syndrome characterized by severe bacteremia, paradoxical hyper-inflammation, universal polymicrobial coinfection and immune dysregulation, and demonstrates that NGS-guided pathogen detection is pivotal for timely diagnosis and improved survival. Larger prospective cohorts are now needed to validate early-alert algorithms and to evaluate targeted removal of anti-IFN-γ autoantibodies and adjunctive immunomodulation, thereby refining therapeutic protocols and reducing mortality.

Ethical Compliance

This study received formal ethics clearance from the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University (Approval Code: 2022-KT-Guike-127). Written informed consent was obtained from all study participants prior to their inclusion in the research. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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