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Role of nemonoxacin as a therapeutic option for community-acquired pneumonia in the era of atypical pathogens

Xiaoping Zhang[a,b], Guoli Mo[a,b], Fengjia Zhu[a,b], Kaiwen Zhang[a,b], Lijie Tian[a,b], Yueran Lv[a,b], Jing Chen[a,b,*]

[a] Research Institute, Zhejiang Medicine Co., Ltd, Shaoxing 312366, China
[b] School of Life Sciences and Biopharmaceuticals, Shenyang Pharmaceutical University, Shenyang 110016, China

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ABSTRACT

Objective: To systematically summarize the clinical data from phase II–IV studies of nemonoxacin malate and comprehensively evaluate the clinical efficacy of nemonoxacin in treating pneumonia caused by atypical pathogens, so as to inform empirical antimicrobial selection in clinical practice.

Methods: A retrospective analysis was performed on the results of four phase II/III clinical studies of nemonoxacin malate in patients with community-acquired pneumonia (CAP) and on the composition and clinical outcomes of atypical pathogen–infected patients in one phase IV clinical study; subgroup efficacy analyses were conducted by age and by presence or absence of co-pathogen infection.

Results: This study included four phase II/III controlled trials and one phase IV single-arm trial, with a primary analysis population of 1769 CAP patients, of whom 994 were male (56.2%) and 775 were female (43.8%), with a mean age of 47.83 ± 16.39 years. In the phase II/III studies, 370 patients (27.8%) were positive for atypical pathogens, including *Mycoplasma pneumoniae* (MP) in 265 cases (19.9%), *Chlamydia pneumoniae* (CP) in 68 cases (5.1%), and *Legionella pneumophila* (LP) in 85 cases (6.4%). In the phase IV study, 172 patients (39.7%) were positive for atypical pathogens, including PM in 141 cases (32.6%), CP in 14 cases (3.2%), and LP in 50 cases (11.5%).Efficacy analysis showed that nemonoxacin 500 mg oral and injectable formulations had clinical success rates against atypical pathogens of 98.0% *vs* levofloxacin 95.5% (oral) and 97.7% *vs* levofloxacin 95.8% (injectable), respectively; against MP the rates were 99.0% *vs* 94.1% (oral) and 97.6% *vs* 100.0% (injectable), respectively, suggesting that the clinical efficacy of the two formulations of nemonoxacin is slightly superior to or comparable with levofloxacin. Additionally, subgroup analyses stratified by age and by presence of co-pathogen infection showed that nemonoxacin demonstrated good clinical efficacy in patients aged both < 60 years and ≥ 60 years, regardless of whether the infection was solely due to atypical pathogens or accompanied by other pathogens.

Conclusion: Nemonoxacin demonstrated good clinical efficacy in CAP patients with atypical pathogen infections, with effects comparable to or superior to levofloxacin, and may be considered as one of the options for empirical CAP treatment or as a therapeutic choice after confirmation of atypical pathogen infection.

Atypical pathogens play an important role in the common respiratory disease CAP, primarily including MP, CP, and LP. In recent years, the proportion of pneumonia due to atypical pathogens has been steadily increasing; notably, MP has replaced *Streptococcus pneumoniae* as the leading causative pathogen of adult CAP in China.[1–4] Multiple epidemiological investigations have revealed a substantial disease burden: in 2007, the average proportion of atypical pathogens in global CAP was approximately 22%,[5] whereas data from parts of China showed that the proportion reached 43.4% during 2008–2010;[6] by 2016–2020, the positive rate in southeastern Beijing remained as high as 40.8%.[7] Because CAP is often treated empirically in clinical practice, the choice of agents targeting atypical pathogens has increasingly become a focus of attention.

Nemonoxacin, a novel non-fluorinated C8-methoxyquinolone, demonstrates strong antibacterial activity against MP (minimum inhibitory concentration [MIC]: 0.03–0.125 mg/L) and CP (MIC:

* Corresponding author.
E-mail address: chenjing@zmc.top (J. Chen).

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0.04–0.36 mg/L).[8,9] It has advantages such as broad-spectrum antibacterial activity and good lung tissue penetration, and shows significant efficacy against atypical pathogen infections.[10]

This paper retrospectively pooled and analyzed the efficacy data of patients with atypical pathogen infections from five clinical studies involving CAP patients; the findings are reported below.

Methods and data

Data

Data for this study were extracted from the clinical study database of Xinchang Pharmaceutical Factory, Zhejiang Medicine Co., Ltd., the holder of nemonoxacin maleate, and included five clinical studies in CAP patients, comprising four phase II/III studies completed between 2011 and 2017 (including two phase II and two phase III studies) and one phase IV study completed between 2018 and 2020, with the phase II and phase III studies using a randomized, double-blind, controlled design, while the phase IV study using a single-arm, open-label design. The overall study designs, subject distributions, and baseline demographic characteristics of each study are shown in Tables 1 and 2.

Methods

This study collected data from the primary analysis populations of five clinical studies, focusing on patients positive for atypical pathogens (defined as positive serology or positive sputum culture for MP), and specifically analyzed that population's distribution, baseline infection symptoms, clinical efficacy, as well as age and concomitant bacterial infections.

Given the study designs, the oral-formulation clinical studies enrolled patients with mild-to-moderate CAP, while the injectable-formulation clinical studies targeted moderate-to-severe patients; the two differed in inclusion criteria and treatment duration. Therefore, in this study, the study data were listed, summarized, and analyzed separately.

Statistical analysis

All statistical analyses in this study were performed using SPSS 26.0; categorical data are presented as numbers (percentages). For key categorical variables, two statistical methods were used in combination: (1) calculate the between-group difference in percentages and its 95% confidence interval (CI) to assess the effect size and precision of the difference; (2) perform a chi-square test for hypothesis testing. All tests were two-sided; differences between groups were considered statistically significant when $P < 0.05$ or when the 95% CI for the rate difference did not include 0.

Results

This study included 1769 CAP patients who met the primary analysis population criteria across five clinical studies, of whom 994 were male (56.2%) and 775 were female (43.8%); the mean age was 47.83 ± 16.39 years, and the majority (70.6%) were under 60 years of age. In the overall population, 542 patients (30.7%) were positive for atypical pathogens at baseline, and the detection rate showed a marked upward trend.

Pathogen distribution: MP was the most common, with 406 cases (23.0%), accounting for 74.9% of all atypical pathogen infections; this was followed by LP with 135 cases (7.6%) and CP with 82 cases (4.6%). Additionally, 171 patients (9.7%) were observed to have co-infections involving atypical pathogens, of whom 106 (6.0%) had combined atypical pathogen and bacterial infections, and 65 (3.7%) had co-infections with multiple atypical pathogens.

Detection of atypical pathogens

The three phase II–IV oral-formulation studies enrolled a total of 1094 patients with mild-to-moderate CAP. In the two pre-marketing phase II/III studies, the primary analysis population totaled 655 patients, of whom 150 (22.9%) were positive for atypical pathogens, including 116 cases of MP (17.7%), 25 cases of CP (3.8%), and 25 cases of LP (3.8%). In the single post-marketing phase IV study, 433 of the 439 patients in the primary analysis population underwent atypical pathogen testing; 172 (39.7%) were positive, including 141 cases of MP (32.6%), 14 cases of CP (3.2%), and 50 cases of LP (11.5%). Statistical results showed that the detection rates of MP and LP were significantly higher in the phase IV study than in the phase II/III studies.

Two phase II/III studies of the injectable formulation enrolled a total of 675 patients with moderate-to-severe CAP; at baseline, 220 (32.6%) were positive for atypical pathogens, including 149 cases of MP (22.1%), 43 cases of CP (6.4%), and 60 cases of LP (8.9%). In the phase II/III studies, the detection rates of the three atypical pathogens were also significantly higher in the injectable formulation studies than in the oral-formulation studies.

Baseline characteristics

The baseline infection symptoms, signs, and laboratory parameters were systemically assessed for all five clinical studies. The baseline characteristics of patients with atypical pathogen infections are shown in Table 3.

The results show that fever was common, with an overall incidence of 91.5%, but there were significant differences between pathogens, with the highest fever rate following MP infection (93.1%), which was

Table 1
Clinical study overview.

Clinical phase/Region	Overall design	Number of subjects		Age (year) Mean ± standard deviation	Sex
		Test group	Control group		
Oral formulation: patients with mild-to-moderate CAP					
Phase II (TG-873870–3); China	Randomized, double-blind, multicenter; qd, 7–10 d	500 mg: 60 750 mg: 56	500 mg : 52	38.77 ± 14.87	Male: 90 (53.6%) Female: 78 (46.4%)
Phase III (TG-873870-C-4); China	Randomized, double-blind, multicenter; qd, 7–10 d	500 mg: 327	500 mg : 160	43.6 ± 14.77	Male: 264 (54.2%) Female: 223 (45.8%)
Phase IV (XCNN-160729–2); China	Single-arm, open-label, multicenter; qd, 7–10 d	500 mg : 439	/	43.5 ± 15.9	Male: 217 (49.4%) Female: 222 (50.6%)
Injectable formulation: patients with moderate-to-severe CAP					
Phase II (TG-873870-C-5); China	Randomized, double-blind, multicenter; qd, 7–14 d	500 mg: 67 650 mg: 64	400 mg:64	52.6 ± 15.14	Male: 124 (63.6%) Female: 71 (36.4%)
Phase III (TG-873870-C-6); China	Randomized, double-blind, multicenter; qd, 7–14 d	500 mg: 314	500 mg:166	57.3 ± 14.33	Male: 299 (62.3%) Female: 181 (37.7%)

Note: The primary analysis population for TG-873870–3 was FAS, and those for the others were mITT sets. Except for the phase II study of the injectable formulation, in which the control group received moxifloxacin 650 mg, the control groups in all other studies received levofloxacin 500 mg.

Table 2
Distribution of atypical pathogens in CAP patients in the nemonoxacin phase II–IV clinical studies.

Distribution of atypical pathogens	Phase II/III clinical studies (oral)[a]					Phase IV clinical study (oral)[b]		Rate difference and 95% CI[c]	*P value*
	N = 387	N = 56	Levofloxacin 500 mg N = 212	Total N = 655	Detection rate (%)	Nemonoxacin 500 mg N = 433	Detection rate (%)		
Atypical pathogens	**89**	**17**	**44**	**150**	**22.9**	**172**	**39.7**	**16.8 [11.2,22.4]**	**< 0.01**
MP	67	15	34	116	17.7	141	32.6	14.9[9.6,20.1]	< 0.01
CP	15	1	9	25	3.8	14	3.2	0.6[-2.8,1.6]	0.612
LP	19	1	5	25	3.8	50	11.5	7.7[4.4,11.1]	**< 0.**.01

Pathogens	Phase II/III clinical studies (injectable)[d]						Rate difference and 95% CI[e]	*P* value
	N = 381	N = 64	Moxifloxacin 400 mg N = 64	Levofloxacin 500 mg N = 166	Total N = 675	Detection rate (%)		
Atypical pathogens	**128**	**19**	**25**	**48**	**220**	**32.6**	**9.7 [4.9,14.5]**	**< 0.01**
MP	82	13	21	33	149	22.1	4.4[0.1,8.6]	0.046
CP	20	7	7	9	43	6.4	2.6[0.2,0.49]	0.035
LP	44	2	2	12	60	8.9	5.1[2.5,7.7]	< 0.01

Note: a A total of 14 cases involved multiple atypical pathogen infections, of which 12 cases involved 2 pathogens and 2 cases involved 3 pathogens; b Six cases did not undergo atypical pathogen testing and were not included in the statistics; a total of 32 cases involved multiple atypical pathogen infections, of which 31 cases involved 2 pathogens and 1 case involved 3 pathogens; c Between-group comparison: phase IV *vs* phases II/III (combined); d A total of 29 cases involved infections with multiple atypical pathogens, of which 27 cases involved two pathogens and 2 cases involved three; e Between-group comparison: phase II/III (combined, injectable formulation) *vs* phase II/III (combined, oral formulation).

significantly higher than the fever rate following LP infection (84.4%). Regarding cough, 98.3% of patients experienced cough, with "occasional cough" and "frequent cough" accounting for 36.7% and 44.3%, respectively. Notably, among patients with MP infection, the proportion with frequent cough or more severe reached 65.3%, and 10.1% of patients had cough severe enough to affect sleep, suggesting that MP infection may cause more intense and persistent coughing symptoms.

In terms of sputum characteristics, 81.5% of patients had sputum volume that was small to moderate (< 50 ml/day), only 10.3% had large amounts, and very large amounts (≥ 100 ml/day) were only 0.4%. The sputum was predominantly mucopurulent; 41.0% of patients presented with "a small amount of pus mixed in mucus," and 17.7% of patients had purulent material accounting for < 1/3. It is noteworthy that 16.1% of patients had purely mucoid sputum or saliva-like sputum, which differs from the purulent sputum characteristic of typical bacterial pneumonia (*e.g.*, *Streptococcus pneumoniae* pneumonia).

In addition, 45.2% of patients experienced dyspnea, with 12.2% having pronounced symptoms; the majority of patients (65.5%) had no chest pain or chest discomfort. Pulmonary auscultation detected moist rales or bronchial sounds in 67.5% of patients.

In laboratory tests, only 30.8% of patients had abnormal white blood cell counts, while 59.4% had neutrophil proportions above 70%. These results indicate that white blood cell count, a conventional screening marker for typical bacterial pneumonia, has insufficient sensitivity in atypical pathogen infections and should not be used as the sole basis for exclusion; they also reflect that atypical pathogen infections can still provoke a significant neutrophilic immune response.

Imaging results showed that all patients with atypical pathogen infections had new inflammatory exudative or infiltrative findings; therefore, even when clinical symptoms are atypical, positive pulmonary imaging remains an indispensable basis for confirming pneumonia.

Analysis of clinical efficacy

This study conducted statistical analyses of clinical efficacy at the Test of Cure (TOC) visit.

In the three oral formulation phase II–IV studies, the mean treatment durations for patients receiving oral nemonoxacin 500 mg and levofloxacin 500 mg were 8.67 ± 1.38 days and 7.89 ± 1.53 days, respectively. In the two injectable formulation phase II–III studies, the mean treatment durations for patients receiving injectable nemonoxacin 500 mg and levofloxacin 500 mg were 9.73 ± 2.34 days and 9.64 ± 2.65 days, respectively.

Efficacy analysis results showed (Table 4) that nemonoxacin 500 mg and levofloxacin 500 mg both demonstrated good clinical efficacy against CAP caused by atypical pathogens. Specifically, the clinical success rates of oral nemonoxacin and levofloxacin against atypical pathogen infections were 98.0% and 95.5%, respectively; for the injectable formulations the rates were 97.7% and 95.8%, respectively. Although between-group differences did not reach statistical significance, the numerical trend indicates that nemonoxacin had a certain advantage in clinical success rate over levofloxacin.

Further pathogen-specific analysis showed that nemonoxacin 500 mg achieved clinical success rates above 96.5% against MP, CP, and LP, confirming its comprehensive coverage and excellent efficacy against atypical pathogens.

Analysis of clinical efficacy across subgroups

(1) Age (< 60 years and ≥ 60 years)

For CAP patients in the nemonoxacin 500 mg groups of the five phase II–IV clinical studies, patients were stratified by age, and the serological positivity rates for atypical pathogens and corresponding clinical efficacy across age groups were analyzed (results shown in Table 5).

In the injectable formulation clinical study with a balanced age distribution, the atypical pathogen positivity rates among CAP patients were 23.9% (79/330) for those ≥ 60 years and 40.9% (141/345) for those < 60 years, suggesting atypical pathogen infections are more common in younger patients. Efficacy analysis showed that nemonoxacin 500 mg demonstrated robust clinical efficacy across age groups: among patients ≥ 60 years, the clinical success rate for nemonoxacin injection was 96.1% versus 93.8% for levofloxacin; among patients < 60 years, the success rates were 98.7% for nemonoxacin and 96.9% for levofloxacin. Although the rate differences between groups and their 95% CIs did not reach statistical significance, the numerical data consistently showed a trend of slightly superior efficacy for nemonoxacin compared with the comparator.

Table 3
Baseline infectious symptoms of clinical CAP patients in the nemonoxacin phase II–IV studies.

Baseline infectious symptom	Oral, phase II–IV								Injectable, phase II/III								Total							
	MP: N = 257		CP: N = 39		LP: N = 75		Subtotal: N = 322		MP: N = 149		CP: N = 43		LP: N = 60		Subtotal: N = 220		MP: N = 406		CP: N = 82		LP: N = 135		Subtotal: N = 542	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Fever																								
Yes	240	93.4	36	92.3	64	85.3	299	92.9	138	92.6	38	88.4	50	83.3	197	89.5	378	93.1	74	90.2	114	84.4	496	91.5
No	17	6.6	3	7.7	11	14.7	23	7.1	11	7.4	5	11.6	10	16.7	23	10.5	28	6.9	8	9.8	21	15.6	46	8.5
Cough																								
No (-)	4	1.6	2	5.1	4	5.3	8	2.5	0	0.0	1	2.3	0	0.0	1	0.5	4	1.0	3	3.7	4	3.0	9	1.7
Occasional (+)	109	42.4	18	46.2	35	46.7	144	44.7	28	18.8	14	32.6	18	30.0	55	25.0	137	33.7	32	39.0	53	39.3	199	36.7
Frequent (++)	103	40.1	15	38.5	24	32.0	121	37.6	89	59.7	20	46.5	31	51.7	119	54.1	192	47.3	35	42.7	55	40.7	240	44.3
Accompanied by chest pain (+++)	19	7.4	3	7.7	7	9.3	26	8.1	13	8.7	6	14.0	5	8.3	19	8.6	32	7.9	9	11.0	12	8.9	45	8.3
Affecting sleep (++++)	22	8.6	1	2.6	5	6.7	23	7.1	19	12.8	2	4.7	6	10.0	26	11.8	41	10.1	3	3.7	11	8.1	49	9.0
Sputum volume[a]																								
No	30	11.7	6	15.4	11	14.7	39	12.1	1	0.7	0	0.0	2	3.3	2	0.9	31	7.6	6	7.3	13	9.6	41	7.6
Small amount: < 10 ml/day	104	40.5	19	48.7	37	49.3	140	43.5	62	41.6	20	46.5	31	51.7	97	44.1	166	40.9	39	47.6	68	50.4	237	43.7
Medium amount ≥ 10, < 50 ml/day	106	41.2	12	30.8	20	26.7	122	37.9	58	38.9	16	37.2	18	30.0	83	37.7	164	40.4	28	34.1	38	28.1	205	37.8
Large amount ≥ 50, < 100 ml/day	16	6.2	2	5.1	7	9.3	20	6.2	26	17.4	7	16.3	9	15.0	36	16.4	42	10.3	9	11.0	16	11.9	56	10.3
Very large amount ≥ 100 ml/day	0	0.0	0	0.0	0	0.0	0	0.0	2	1.3	0	0.0	0	0.0	2	0.9	2	0.5	0	0.0	0	0.0	2	0.4
Sputum nature[a]																								
No	32	12.5	6	15.4	11	14.7	41	12.7	1	0.7	0	0.0	2	3.3	2	0.9	33	8.1	6	7.3	13	9.6	43	7.9
Saliva or purely mucoid	32	12.5	6	15.4	13	17.3	43	13.4	26	17.4	12	27.9	11	18.3	44	20.0	58	14.3	18	22.0	24	17.8	87	16.1
Mucoid sputum with a small amount of purulence	107	41.6	16	41.0	34	45.3	136	42.2	60	40.3	15	34.9	25	41.7	86	39.1	167	41.1	31	37.8	59	43.7	222	41.0
Purulent < 1/3	44	17.1	8	20.5	5	6.7	51	15.8	26	17.4	10	23.3	16	26.7	45	20.5	70	17.2	18	22.0	21	15.6	96	17.7
Purulent > 1/3	22	8.6	2	5.1	7	9.3	27	8.4	17	11.4	0	0.0	5	8.3	21	9.5	39	9.6	2	2.4	12	8.9	48	8.9
Purulent > 2/3	19	7.4	1	2.6	5	6.7	23	7.1	19	12.8	6	14.0	1	1.7	22	10.0	38	9.4	7	8.5	6	4.4	45	8.3
Dyspnea/tachypnea																								
No (-)	193	75.1	26	66.7	44	58.7	234	72.7	40	26.8	11	25.6	25	41.7	63	28.6	233	57.4	37	45.1	69	51.1	297	54.8
Mild (+)	55	21.4	10	25.6	28	37.3	76	23.6	73	49.0	19	44.2	21	35.0	103	46.8	128	31.5	29	35.4	49	36.3	179	33.0
Marked (++)	9	3.5	3	7.7	3	4.0	12	3.7	36	24.2	13	30.2	14	23.3	54	24.5	45	11.1	16	19.5	17	12.6	66	12.2
Chest pain or chest discomfort																								
Without chest pain	156	60.7	25	64.1	33	44.0	190	59.0	112	75.2	32	74.4	44	73.3	165	75.0	268	66.0	57	69.5	77	57.0	355	65.5
With chest pain	101	39.3	14	35.9	42	56.0	132	41.0	37	24.8	11	25.6	16	26.7	55	25.0	138	34.0	25	30.5	58	43.0	187	34.5
Moist rales or bronchial sounds[b]																								
No (-)	105	40.9	11	28.2	37	49.3	129	40.1	34	22.8	9	20.9	9	15.0	46	20.9	139	34.2	20	24.4	46	34.1	175	32.3
Mild (+)	109	42.4	19	48.7	28	37.3	139	43.2	69	46.3	18	41.9	25	41.7	98	44.5	178	43.8	37	45.1	53	39.3	237	43.7
Marked (++)	42	16.3	9	23.1	10	13.3	53	16.5	46	30.9	16	37.2	26	43.3	76	34.5	88	21.7	25	30.5	36	26.7	129	23.8
White blood cell count (WBC) : **> 10,000/mm**3 or **< 4000/mm**3 (phase II/III) , > 95,000/mm3 or < 3500/mm3 (phase IV)																								
No	189	73.5	29	74.4	47	62.7	229	71.1	106	71.1	28	65.1	38	63.3	146	66.4	295	72.7	57	69.5	85	63.0	375	69.2
Yes	68	26.5	10	25.6	28	37.3	93	28.9	43	28.9	15	34.9	22	36.7	74	33.6	111	27.3	25	30.5	50	37.0	167	30.8
Neutrophil: **> 70%** (phase II/III), ≥ 75% (phase IV)																								
No	180	70.0	21	53.8	52	69.3	215	66.8	73	49.0	14	32.6	36	60.0	107	48.6	253	62.3	35	42.7	88	65.2	322	59.4
Yes	77	30.0	18	46.2	23	30.7	107	33.2	76	51.0	29	67.4	24	40.0	113	51.4	153	37.7	47	57.3	47	34.8	220	40.6
Is there new inflammatory exudate or infiltrate on imaging																								
No	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Yes	257	100.0	39	100.0	75	100.0	322	100.0	149	100.0	43	100.0	60	100.0	220	100.0	406	100.0	82	100.0	135	100.0	542	100.0

Note: a In one case in the oral formulation clinical study, the examination was not performed; b Oral phase II: moist rales; oral phase III and injectable phase II/III: abnormal auscultatory findings such as bronchial sounds and/or localized moist rales; phase IV: dullness to percussion, bronchial sounds or wheeze on auscultation; in one case in the oral formulation clinical study, the examination was not performed.

Table 4
Summary of clinical efficacy in patients with atypical pathogen pneumonia across five clinical studies (TOC visit).

Clinical success rat%	Oral: phase II–IV					Injectable: phase II–III				
	Nemonoxacin 500 mg	Levofloxacin 500 mg	Total	Rate difference and 95% CI	*P value*	Nemonoxacin 500 mg	Levofloxacin 500 mg	Total	Rate difference and 95% CI	*P value*
Atypical pathogens	**98.0 (242/247)**	**95.5 (42/44)**	**97.6 (284/291)**	**2.5 [-3.9,8.9]**	**0.315**	**97.7 (125/128)**	**95.8 (46/48)**	**97.2(171/176)**	**1.8 [-4.4,8.1]**	**0.517**
MP	99.0 (194/196)	94.1 (32/34)	98.3 (226/230)	4.9 [-3.2,12.9]	0.045	97.6 (80/82)	100.0 (33/33)	98.3 (113/115)	-2.4 [-5.8,0.9]	0.365
CP	96.6 (28/29)	- (9/9)	97.4 (37/38)	-	-	100.0 (20/20)	- (8/9)	96.6 (28/29)	-	-
LP	96.9 (63/65)	- (5/5)	97.1 (68/70)	-	-	97.7 (43/44)	91.7 (11/12)	96.4 (54/56)	6.1 [-10.2,22.3]	0.316

Note: The efficacy for patients without efficacy assessment and in the oral nemonoxacin 750 mg, injectable nemonoxacin 650 mg, and moxifloxacin 400 mg dose groups were not included in the analysis; Between-group difference comparison: nemonoxacin 500 mg *vs* levofloxacin 500 mg; When the case number was < 10, success rate and rate difference were not calculated.

Table 5
Comparison of clinical efficacy in atypical-pathogen pneumonia patients of different ages from five clinical studies (TOC visit).

Clinical success rat%	Oral: phase II–IV					Injectable: phase II–III				
	Nemonoxacin 500 mg	Levofloxacin 500 mg	Total	Rate difference and 95% CI	*P value*	Nemonoxacin 500 mg	Levofloxacin 500 mg	Total	Rate difference and 95% CI	*P value*
≥ 60 years	94.1 (32/34)	100.0 (7/7)	95.1 (39/41)	-0.59 [-13.8,2.0]	0.511	96.1 (49/51)	93.8 (15/16)	95.5 (64/67)	2.3 [-10.7,15.3]	0.694
< 60 years	98.6 (210/213)	94.6 (35/37)	98.0 (245//250)	4.0 [-3.5,11.5]	0.109	98.7 (76/77)	96.9 (31/32)	98.2 (107/109)	1.8 [-4.7,8.4]	0.518

Note: The efficacy for patients without efficacy assessment and in the oral nemonoxacin 750 mg, injectable nemonoxacin 650 mg, and moxifloxacin 400 mg dose groups were not included in the analysis; Between-group comparison: nemonoxacin 500 mg *vs* levofloxacin 500 mg.

(2) Infection types

A pooled analysis was conducted on the types of pathogen infections in CAP patients across the five clinical studies (results are shown in Table 6). Among the 1763 patients included in the analysis, 436 (24.7%) had infections caused solely by atypical pathogens, which exceeded the number of sole bacterial infections (361; 20.5%) and bacterial combined with atypical pathogen infections (106; 6.0%). Overall, the total number of atypical pathogen infections (including sole and mixed infections) was 542, yielding an overall positivity rate of 30.7%.

Across different types of clinical studies, in the phase II/III studies of the oral and injectable formulations, the baseline bacterial culture positivity rates were both > 30.0%, with the incidence of bacterial combined with atypical pathogen infections being 7.5% and 8.0%, respectively. In the phase IV study, because sputum specimen collection was not mandatory, the baseline bacterial positivity rate was generally low (3.5%). Regarding atypical pathogen detection, the positivity rates in the phase II/III studies of the oral and injectable formulations were 22.9% and 32.6%, respectively, while in the phase IV study, the rates reached 39.7%; considering the chronological order of the clinical trials, these results indicate an increasing trend in atypical pathogen infection rates.

The clinical efficacy results for patients with CAP caused by different pathogen types (see Table 7) indicate that, regardless of oral or injectable formulation, nemonoxacin's clinical efficacy against sole atypical pathogen infections (97.6%–100.0%) was significantly higher than its efficacy against sole bacterial infections (87.6%–93.4%) and bacterial combined with atypical pathogen infections (88.2%–97.3%). The levofloxacin group showed the same trend.

In terms of formulation differences, nemonoxacin 500 mg injection achieved a clinical efficacy rate of 97.3% for bacterial combined with atypical pathogen infections, outperforming the oral formulation in this population.

Discussion

This study, based on data from a series of phase II–IV clinical trials of nemonoxacin in patients with CAP, systematically analyzed the epidemiological features and clinical characteristics of atypical pathogens as well as nemonoxacin's efficacy, yielding the following key findings and implications.

The infection rate of atypical pathogens continues to rise, and increasing resistance exacerbates challenges to empirical therapy

Pooled analysis in this study showed that the overall positivity rate of atypical pathogens in CAP reached 30.7%. Notably, from the earlier phase II/III studies to the more recent phase IV studies, the detection rate of atypical pathogens showed a clear upward trend (for oral formulation, it increased from 22.9% to 39.7%). This phenomenon is consistent with recent reports worldwide, particularly in Asia, of increased detection rates of atypical pathogens such as MP.[5–7] This study further confirmed that MP (23.0%, 406/1763) has far surpassed *Streptococcus pneumoniae* (5.2%, 92/1763), becoming one of the main causative pathogens in adult CAP in China. Meanwhile, resistance to commonly used drugs such as macrolides has become increasingly prominent,[1,11,12] and resistance rates in MP in particular have continued to rise,[13,14] increasing the risk of treatment failure. Therefore, in the initial empirical treatment phase, it is especially critical to select antimicrobial drugs that effectively cover atypical pathogens and can mitigate the risk of resistance.[15]

Table 6
Distribution of CAP patients with different types of pathogen infections across five clinical studies.

Type of pathogen infection	Oral				Injectable	
	Phase II/III (N = 655)		Phase IV (N = 433)		Phase II/III (N = 675)	
	n	%	n	%	n	%
Sole bacterial infection	**196**	**29.9**	**12**	**2.8**	**153**	**22.7**
Sole atypical pathogen infection	**101**	**15.4**	**169**	**39.0**	**166**	**24.6**
Single atypical pathogen	88	13.4	137	31.6	146	21.6
Multiple atypical pathogens	13	2.0	32	7.4	20	3.0
MP + CP	7	1.1	2	0.5	10	1.5
MP + LP	4	0.6	26	6.0	9	1.3
CP + LP	1	0.2	3	0.7	0	0
MP + CP + LP	1	0.2	1	0.2	1	0.1
Mixed infection (bacterial + atypical pathogens)	**49**[a]	**7.5**	**3**	**0.7**	**54**[b]	**8.0**
Atypical pathogens + *Klebsiella pneumoniae*	16	2.4	0	0.0	19	2.8
Atypical pathogens + *Haemophilus influenzae / Haemophilus parainfluenzae*	7	1.1	0	0.0	15	2.2
Atypical pathogens + *Streptococcus pneumoniae*	8	1.2	1	0.2	9	1.3
Atypical pathogens + *Staphylococcus aureus*	8	1.2	0	0.0	3	0.4
Atypical pathogens + *Pseudomonas aeruginosa*	1	0.2	0	0.0	3	0.4
Atypical pathogens + *Acinetobacter baumannii*	2	0.3	0	0.0	3	0.4
Atypical pathogens + Others	7	1.1	2	0.5	3	0.4

Note: a Includes 1 case with 3 atypical pathogens + 1 bacterium; b Includes 8 cases with 2 atypical pathogens + 1 bacterium, 1 case with 3 atypical pathogens + 1 bacterium, 1 case with 2 atypical pathogens + 2 bacteria, and 1 case with 1 atypical pathogen + 2 bacteria.

Table 7
Comparison of clinical efficacy among CAP patients with different infection types across five clinical studies (TOC visit).

Infection type		Oral: phase II–IV			Injectable: phase II–III		
		Nemonoxacin 500 mg N = 820	Levofloxacin 500 mg N = 212	Total N = 1032	Nemonoxacin 500 mg N = 381	Levofloxacin 500 mg N = 166	Total N = 547
Sole bacterial infection	Detection rat%	15.1 (124/820)	31.6 (67/212)	18.5 (191/1032)	26.2 (100/381)	13.9 (23/166)	22.5 (123/547)
	Clinical success rat%	93.4 (114/122)	89.2 (58/65)	92.0 (172/187)	87.6 (85/97)	90.9 (20/22)	88.2 (105/119)
Single atypical pathogen infection	Detection rat%	22.7 (186/820)	11.3 (24/212)	20.3 (210/1032)	21.5 (82/381)	21.7 (36/166)	21.6 (118/547)
	Clinical success rat%	99.4 (173/174)	95.8 (23/24)	99.0 (196/198)	97.6 (80/82)	94.4 (34/36)	96.6 (114/118)
Multiple atypical pathogens infection	Detection rat%	5.0 (41/820)	1.9 (4/212)	4.4 (45/1032)	2.4 (9/381)	3.0 (5/166)	2.6 (14/547)
	Clinical success rat%	100.0 (39/39)	- (4/4)	100.0 (43/43)	- (9/9)	- (5/5)	100.0 (14/14)
Bacteria + atypical pathogen infection	Detection rat%	4.1 (34/820)	7.5 (16/212)	4.8 (50/1032)	9.7 (37/381)	4.2 (7/166)	8.0 (44/547)
	Clinical success rat%	88.2 (30/34)	93.8 (15/16)	90.0 (45/50)	97.3 (36/37)	- (7/7)	97.7 (43/44)

Note: The efficacy for patients without efficacy assessment and in the oral nemonoxacin 750 mg, injectable nemonoxacin 650 mg, and moxifloxacin 400 mg dose groups were not included in the analysis; When the case number was < 10, success rate was not calculated.

Clinical presentations of atypical pathogen infections are non-classical, and conventional inflammatory markers lack sufficient sensitivity

This study and multiple reports indicate that the clinical manifestations of atypical pathogen infections differ significantly from those of typical bacterial pneumonia; patients often present with an irritating dry cough or cough up small amounts of mucoid sputum, which contrasts sharply with the rust-colored purulent sputum caused by typical bacteria such as *Streptococcus pneumoniae*.[16,17]

In laboratory testing, only about 30.8% of patients showed elevated white blood cell counts, indicating that white blood cell count—as a traditional screening marker for bacterial infection—has markedly insufficient sensitivity in atypical pathogen infections; relying solely on a normal white blood cell count to exclude bacterial infection or to withhold antimicrobial therapy readily leads to missed diagnoses and treatment delays. By contrast, all patients exhibited pulmonary imaging infiltrates, underscoring the cornerstone role of imaging in the diagnosis of CAP.

Nemonoxacin demonstrates broad-spectrum, potent efficacy, and its safety profile and formulation options confer notable clinical value

Nemonoxacin's clinical efficacy against the three major atypical pathogens (MP, CP, and LP) each exceeds 96.5%. Especially in clinically challenging mixed infections of typical bacteria and atypical pathogens, the injectable formulation also achieved an excellent efficacy rate of 97.3%. This is closely related to its excellent lung tissue penetration,[10] ensuring that effective drug concentrations are reached at the site of infection.

Beyond efficacy, its safety advantages are notable: as a novel non-fluorinated respiratory quinolone, nemonoxacin has not, to date,

been reported to cause phototoxicity, tendon rupture, significant hepatotoxicity, or central nervous system adverse reactions associated with conventional fluoroquinolones.[18] Its favorable safety and tolerability make it suitable for special populations such as the elderly and patients with hepatic or renal impairment.[18,19] Consequently, nemonoxacin has been listed in authoritative guidelines as a recommended treatment for CAP caused by MP and CP.[20]

In addition, nemonoxacin is available in both oral and injectable formulations, both of which have demonstrated significant efficacy against CAP and facilitate "sequential therapy," enabling seamless transition from intravenous treatment during severe infection to oral therapy during the stabilization phase, thereby optimizing the treatment course. Besides its confirmed efficacy against the three major atypical pathogens, existing clinical case reports have suggested it may also have therapeutic potential against *Chlamydia psittaci*,[21] which warrants further investigation.

Age influences the distribution of atypical pathogens; nemonoxacin demonstrates reliable efficacy across all age groups

Analysis showed that the atypical pathogen infection rate in CAP patients $<$ 60 years (40.9%) was significantly higher than in those aged $\geq$ 60 years (23.9%). This is consistent with the pathogen distribution trends reported in primary-care CAP diagnosis and treatment guidelines.[16] Although the infection rate in elderly patients is lower,[1,22,23] their clinical presentation is often more insidious, they face a higher risk of complications, and they frequently have comorbid conditions, making drug selection a matter of balancing efficacy and safety. Nemonoxacin demonstrated excellent efficacy in both age groups, and combined with its favorable safety profile, it has become one of the ideal treatment options for patients of all ages—particularly the elderly or those with CAP complicated by multiple pathogen infections.

Summary and prospect

This study, based on large-sample clinical data, confirms that atypical pathogens are playing an increasingly prominent role in the etiological composition of CAP; their clinical manifestations are atypical and pose challenges to traditional diagnostic indicators. As a novel non-fluorinated quinolone, nemonoxacin—by virtue of its excellent clinical efficacy against atypical pathogens (including sole and mixed infections), favorable safety advantages, convenient sequential-therapy formulations, and broad applicability to special populations—offers a new therapeutic option in light of the current shifts in the CAP pathogen spectrum and resistance landscape.

Against the backdrop of rising incidence and resistance rates among atypical pathogens, nemonoxacin can serve as an empirical treatment for CAP and is particularly one of the preferred drugs for patients with suspected or confirmed atypical pathogen infection. Future research will continue to monitor the epidemiology and evolving antimicrobial resistance of atypical pathogens and further validate nemonoxacin's efficacy and cost-effectiveness across diverse clinical settings.

Declarations

Not applicable.

CRediT authorship contribution statement

Xiaoping Zhang: Conceptualization, Data curation, Formal analysis, Writing - original draft preparation. Guoli Mo: Methodology, Investigation, Data curation. Fengjia Zhu: Investigation, Data curation, Validation. Kaiwen Zhang: Investigation, Resources, Validation. Lijie Tian: Data curation, Software, Formal analysis. Yueran Lv: Investigation, Resources. Jing Chen: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Huashan Hospital Fudan University (Approval No. 2017-366). All study participants have signed informed consent forms.

Consent for publication

All authors have read and agreed to the published version of the manuscript and give their consent for publication in this journal.

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