病 院 年 報

2025 年度実績

国立病院機構 あわら病院

========== INDEX ==========

国立病院機構あわら病院の基本方針と使命

基本方針（policy）

『多くの人の笑顔のために』

使命（mission）

・重症心身障がい、難病、長寿医療を柱とし、地域に密着した専門医療を提供します。

・社会的なアプローチを組み入れ、患者中心の心あたたまる医療を実施します。

・臨床研究、教育研修、安全管理をとおして、常により質の高い医療を追求します。

・公益性を確保し、効率的で自立した病院経営を推進します。

あわら病院の概要

1．所在地　　〒910-4272　福井県あわら市北潟 238-1
電話　0776-79-1211　　ＦＡＸ　0776-79-1249
ホームページ　https://awara.hosp.go.jp

2.環境及び交通

あわら病院は、福井県の最北端で石川県境に隣接するあわら市（人口約２８千人）に所在し、南は越前加賀海岸国定公園に指定されている北潟湖に、北は日本海に面する丘陵地帯に立地している。晴れた日には遠く白山連峰を遠望することができ、また、眼下には北潟湖が広がる恵まれた自然の中で、院内は桜を初めとした豊かな木々に恵まれており、閑静で快適な医療環境にある。

当院へのアクセスとしては、2024 年 3 月に北陸新幹線の東京－敦賀間が開業され、芦原温泉駅から東京駅まで直通で約 3 時間となった。飛行機では約 2 時間である。大阪駅からは、特急（サンダーバード）敦賀駅で乗り換え、北陸新幹線を利用して約 2 時間、名古屋駅からは、特急（しらさぎ）敦賀駅で乗り換え、北陸新幹線を利用して約 2 時間、高速道路では大阪から 4 時間、名古屋から 3 時間となる。

※ ＪＲ北陸本線「芦原温泉駅」より約 8km、えちぜん鉄道「あわら湯のまち駅」より約 5km

※ タクシー又はあわら市乗合タクシー　10 分～15 分

3．沿　革

当院は、昭和１４年５月に福井県における結核医療の拠点病院として、県立療養所北潟臨湖園の　名称で創設された。後に、昭和２２年４月には厚生省に移管されて、国立療養所北潟臨湖園として再発足している。その後、平成１６年４月１日に独立行政法人に移行し、国立病院機構あわら病院となった。現病棟は平成２４年３月に竣工し、３個病棟１７２床で運営している。

昭和１４年	５月	福井県立療養所北潟臨湖園として創設。病床数１３２床。
昭和１５年１０月		外気病棟､健康保険委託病棟増築により病床数１８７床となる。
昭和１８年	４月	日本医療団に移管され日本医療団北潟臨湖園となる。
昭和１９年	４月	健康保険連合会病棟及び増築により病床数４００床となる。
昭和２２年	４月	厚生省に移管し、国立療養所北潟臨湖園、県立勝山保養所を分院として併設。
昭和２３年	６月	福井大震災のため建物が崩壊、近隣施設に患者を移転した。
昭和２４年	９月	勝山分院を廃止。
昭和５０年	４月	重症心身障害児（者）病棟新築により、受入れを開始。

昭和５８年	４月	国立療養所北潟病院に名称変更。
平成１５年	１月	第三病棟（結核）の廃止により医療法病床数１８０床となる。
平成１６年	４月	独立行政法人に移行、独立行政法人国立病院機構あわら病院となる。
平成１８年	４月	一般病床１００床のうち、４０床を療養(型)病床に種別変更。
平成２１年１１月		療養病床４０床を障害者病床に種別変更。
平成２４年	３月	病棟集約により医療法病床数１７２床となる。
平成２６年１０月		在宅療養支援病院として認定。
平成２６年１１月		一般病床５２床のうち６床を地域包括ケア病床として届出。
平成２７年	１月	地域包括ケア病床を１０床に増床（一般４２床）。
平成２７年	７月	あわら病院訪問看護ステーションアイリスを開設。
平成２８年	３月	地域包括ケア病床を１２床に増床（一般４０床）。
平成３０年１０月		地域包括ケア病床を１８床に増床（一般３４床）。
令和　２年	１月	一般病床３４床を障害者病床に種別変更。
令和　６年	１０月	地域包括ケア病床を１４床に減床（一般３８床）。
令和　７年	４月	重症心身障害児（者）病棟開設５０周年。

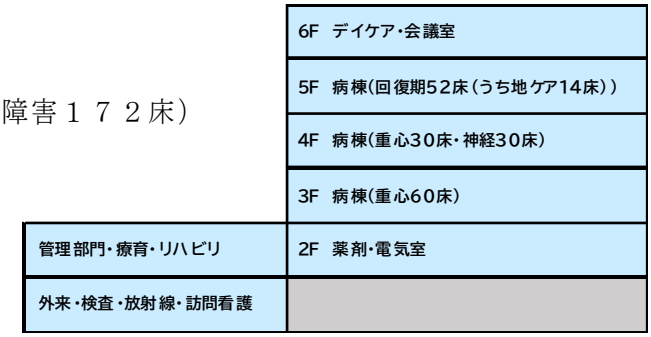
４．標榜診療科

内科、リウマチ科、血液・腫瘍内科、神経内科、老年内科、循環器科、小児科、外科、整形外科、皮膚科、眼科、リハビリテーション科（１２診療科）

※下線は非常勤医師で対応

５．病床数

医療法病床数	１７２床（障害１７２床）
うち 重症心身障害児（者）	９０床
神経難病	３０床
回復期	５２床



６．職員数及び組織

1)　職員数　　１９７名（常勤　１６４名、非常勤　３３名）

（令和７年４月１日現在）　医　師　　８名（常勤７名、非常勤１名）

看護師　１００名（常勤９５名、非常勤５名）

コメディカル　２６名、事務１３名、福祉１０名、療養１３名

令和7年度　外来患者数(診療科目別)

診療科	項目	令和6年度累計	令和7年4月	5月	6月	7月	8月	9月	10月	11月	12月	令和8年1月	2月	3月	令和7年度累計	前年比
内科	延べ患者数	2,055	150	172	154	153	160	161	176	135	168	156	151	155	1,891	△ 164
	初診患者数	434	19	33	18	15	46	22	25	19	27	41	34	14	313	△ 121
	1日平均患者数	8.5	7.1	8.6	7.3	7.0	8.0	8.1	8.0	7.5	8.0	8.2	8.4	7.4	7.8	△ 1
小児科	延べ患者数	1,668	147	156	131	118	111	123	113	128	129	99	122	123	1,500	△ 168
	初診患者数	214	22	16	10	9	11	10	8	19	15	8	19	6	153	△ 61
	1日平均患者数	6.9	7.0	7.8	6.2	5.4	5.6	6.2	5.1	7.1	6.1	5.2	6.8	5.9	6.2	△ 1
循環器科	延べ患者数	413	29	46	24	22	26	27	22	32	26	22	22	29	327	△ 86
	初診患者数	4	0	0	0	0	0	0	0	0	0	1	0	0	1	△ 3
	1日平均患者数	1.7	1.4	2.3	1.1	1.0	1.3	1.4	1.0	1.8	1.2	1.2	1.2	1.4	1.3	△ 0
外科	延べ患者数	221	3	5	6	9	3	4	2	4	1	4	2	1	44	△ 177
	初診患者数	74	1	2	4	5	2	2	1	2	0	3	1	1	24	△ 50
	1日平均患者数	0.9	0.1	0.3	0.3	0.4	0.2	0.2	0.1	0.2	0.0	0.2	0.1	0.0	0.2	△ 1
整形外科	延べ患者数	346	34	23	29	19	23	22	26	10	26	27	11	25	275	△ 71
	初診患者数	4	1	1	1	1	0	1	0	0	0	1	0	1	7	3
	1日平均患者数	1.4	1.6	1.2	1.4	0.9	1.2	1.1	1.2	0.6	1.2	1.4	0.6	1.2	1.1	△ 0
皮膚科	延べ患者数	205	9	13	12	19	21	12	18	26	21	13	18	22	204	△ 1
	初診患者数	20	0	1	2	1	2	0	3	5	1	0	2	1	18	△ 2
	1日平均患者数	0.8	0.4	0.7	0.6	0.9	1.1	0.6	0.8	1.4	1.0	0.7	1.0	1.0	0.8	△ 0
眼科	延べ患者数	41	6	10	5	5	3	2	5	2	5	2	6	2	53	12
	初診患者数	10	2	5	1	1	0	0	0	1	1	1	2	0	14	4
	1日平均患者数	0.2	0.3	0.5	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0.1	0.3	0.1	0.2	0
リウマチ科	延べ患者数	1308	115	108	115	120	108	105	128	85	109	108	106	111	1,318	10
	初診患者数	18	1	0	0	2	0	0	1	0	0	0	1	0	5	△ 13
	1日平均患者数	5.4	5.5	5.4	5.5	5.5	5.4	5.3	5.8	4.7	5.2	5.7	5.9	5.3	5.4	0
神経内科	延べ患者数	152	10	14	8	7	14	6	21	9	5	10	7	11	122	△ 30
	初診患者数	1	1	0	0	1	0	0	0	0	0	0	1	0	3	2
	1日平均患者数	0.6	0.5	0.7	0.4	0.3	0.7	0.3	1.0	0.5	0.2	0.5	0.4	0.5	0.5	△ 0
血液内科	延べ患者数	307	26	26	23	24	24	22	35	25	33	29	28	22	317	10
	初診患者数	0	1	0	0	0	2	1	1	1	1	0	0	0	7	7
	1日平均患者数	1.3	1.2	1.3	1.1	1.1	1.2	1.1	1.6	1.4	1.6	1.5	1.6	1.0	1.3	0
老年内科	延べ患者数	190	15	21	6	14	12	13	12	8	14	15	12	5	147	△ 43
	初診患者数	0	0	2	0	2	0	1	1	0	0	1	0	0	7	7
	1日平均患者数	0.8	0.7	1.1	0.3	0.6	0.6	0.7	0.5	0.4	0.7	0.8	0.7	0.2	0.6	△ 0
計	延べ患者数	6,906	544	594	513	510	505	497	558	464	537	485	485	506	6,198	△ 708
	初診患者数	779	48	60	36	37	63	37	40	47	45	56	60	23	552	△ 227
	1日平均患者数	28.4	25.9	29.7	24.4	23.2	25.3	24.9	25.4	25.8	25.6	25.5	26.9	24.1	25.5	△ 3

令和7年度　入院患者数(診療科目別)

診療科	項目	令和6年度累計	令和7年4月	5月	6月	7月	8月	9月	10月	11月	12月	令和8年1月	2月	3月	令和7年度累計	前年比
内科・循環器科	延べ患者数	2,279	144	248	153	234	280	196	141	122	125	112	219	259	2,233	△ 46
	新入院患者数	58	4	7	4	7	9	3	5	4	5	5	9	5	67	9
	1日平均患者数	6.2	4.8	8.0	5.1	7.5	9.0	6.5	4.5	4.1	4.0	3.6	7.8	8.4	6.1	△ 0.1
老年内科	延べ患者数	6,537	424	432	520	588	559	511	540	541	594	445	522	597	6,273	△ 264
	新入院患者数	9	12	6	13	13	9	11	4	10	9	9	11	4	111	102
	1日平均患者数	17.9	14.1	13.9	17.3	19.0	18.0	17.0	17.4	18.0	19.2	14.4	18.6	19.3	17.2	△ 0.7
神経内科	延べ患者数	11,682	949	973	1096	1,126	1,098	1,141	1,124	1,132	1,215	1,215	1,089	1,219	13,377	1695
	新入院患者数	3	2	6	5	2	6	4	6	3	3	4	4	1	46	43
	1日平均患者数	32.0	31.6	31.4	36.5	36.3	35.4	38.0	36.3	37.7	39.2	39.2	38.9	39.3	36.6	4.6
小児科	延べ患者数	33,368	2,710	2,789	2,717	2,776	2,785	2,714	2,837	2,687	2,771	2,775	2,481	2,736	32,778	△ 590
	新入院患者数	11	6	8	10	9	12	15	12	9	15	10	10	8	124	113
	1日平均患者数	91.4	90.3	90.0	90.6	89.5	89.8	90.5	91.5	89.6	89.4	89.5	88.6	88.3	89.8	△ 1.6
リウマチ科・血液内科	延べ患者数	3,695	247	226	249	283	350	325	402	398	417	339	352	419	4,007	312
	新入院患者数	2	4	4	6	7	5	3	9	10	5	4	6	5	68	66
	1日平均患者数	10.1	8.2	7.3	8.3	9.1	11.3	10.8	13.0	13.3	13.5	10.9	12.6	13.5	11.0	0.9
外科	延べ患者数	1	0	0	0	0	0	0	0	0	0	0	0	0	0	△ 1
	新入院患者数	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1日平均患者数	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
計	延べ患者数	57,562	4,474	4,668	4,735	5,007	5,072	4,887	5,044	4,880	5,122	4,886	4,663	5,230	58,668	1106
	新入院患者数	83	28	31	38	38	41	36	36	36	37	32	40	23	416	333
	1日平均患者数	157.7	149.1	150.6	157.8	161.5	163.6	162.9	162.7	162.7	165.2	157.6	166.5	168.7	160.7	3.0

外来患者数・年齢別　構成比率

集計区分	R6年度	R7年度	前年比
0日～28日	0.0%	0.0%	0.0%
29日～2歳未満	1.3%	0.0%	-1.3%
2歳～4歳未満	1.0%	6.3%	5.3%
4歳～6歳未満	2.7%	0.0%	-2.7%
6歳～10歳未満	3.9%	0.0%	-3.9%
10歳～20歳未満	4.8%	0.5%	-4.3%
20歳～30歳未満	4.2%	5.3%	1.1%
30歳～40歳未満	6.6%	11.1%	4.5%
40歳～50歳未満	9.7%	11.6%	1.9%
50歳～60歳未満	7.9%	2.2%	-5.7%
60歳～65歳未満	5.8%	1.2%	-4.6%
65歳～70歳未満	7.3%	5.1%	-2.2%
70歳～75歳未満	10.4%	5.5%	-4.8%
75歳～80歳未満	10.1%	7.0%	-3.1%
80歳～85歳未満	10.4%	13.5%	3.1%
85歳～90歳未満	8.1%	13.0%	4.9%
90歳～95歳未満	4.6%	13.0%	8.4%
95歳～100歳未満	1.3%	3.6%	2.3%
100歳以上	0.1%	1.2%	1.1%

入院患者数・年齢別　構成比率

集計区分	R6年度	R7年度	前年比
0日～28日	0.0%	0.0%	0.0%
29日～2歳未満	0.7%	0.0%	-0.7%
2歳～4歳未満	0.0%	6.2%	6.2%
4歳～6歳未満	0.0%	0.0%	0.0%
6歳～10歳未満	1.3%	0.0%	-1.3%
10歳～20歳未満	3.3%	0.5%	-2.8%
20歳～30歳未満	8.6%	5.2%	-3.3%
30歳～40歳未満	12.5%	11.2%	-1.3%
40歳～50歳未満	11.8%	12.2%	0.3%
50歳～60歳未満	17.1%	2.2%	-14.9%
60歳～65歳未満	6.6%	1.2%	-5.3%
65歳～70歳未満	5.9%	4.7%	-1.2%
70歳～75歳未満	7.9%	6.2%	-1.7%
75歳～80歳未満	5.3%	7.7%	2.4%
80歳～85歳未満	5.3%	11.4%	6.2%
85歳～90歳未満	7.2%	13.4%	6.2%
90歳～95歳未満	4.6%	12.2%	7.6%
95歳～100歳未満	2.0%	4.5%	2.5%
100歳以上	0.0%	1.0%	1.0%

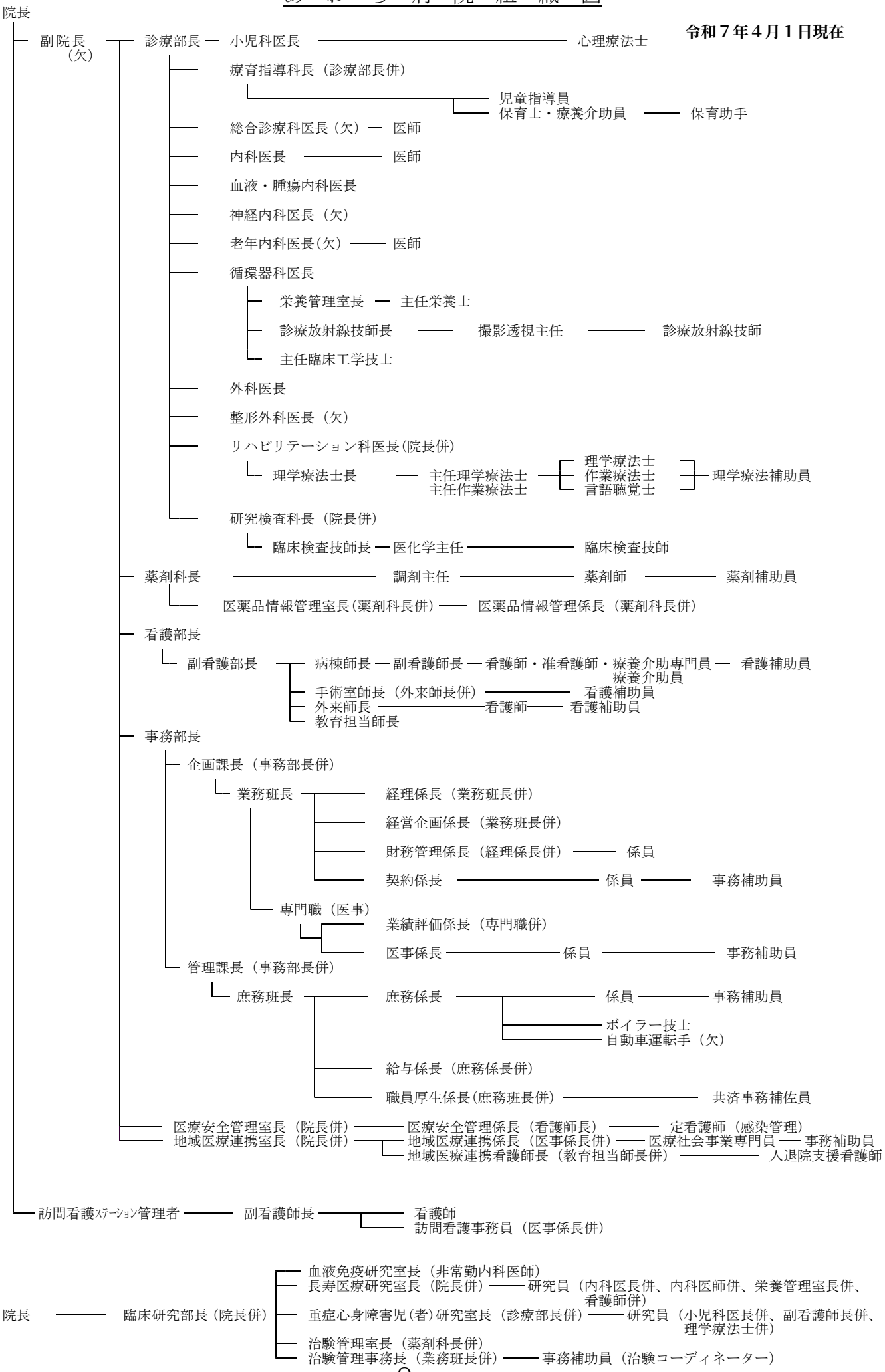
患者市町村別分布

令和7年度

市町村名			入院(累　計)						外　来(累　計)		人　口
			一般患者数	割合　%	重心患者数	割合　%	入院計	割合　%	患者数	割合　%	R7.10.1時点
福井県	二次医療圏	あわら市	10,812	42.3	9,142	27.7	19,954	34.1	4,034	65.0	25,847
		坂井市	6,522	25.5	2658	8.1	9,180	15.7	1,526	24.6	85,464
		福井市	3,287	12.8	6894	20.9	10,181	17.4	357	5.8	252,733
		吉田郡永平寺町	619	2.4	964	2.9	1,583	2.7	94	1.5	18,140
		2次医療圏小計	21,240	83.0	19,658	59.6	40,898	69.8	6,011	96.9	382,184
	その他県内	大野市	562	2.2	2,555	7.7	3,117	5.3	21	0.3	28,165
		鯖江市	0	0.0	1,255	3.8	1,255	2.1	32	0.5	67,035
		越前市	136	0.5	1,879	5.7	2,015	3.4	52	0.8	78,312
		敦賀市	667	2.6	730	2.2	1,397	2.4	32	0.5	60,955
		丹生郡越前町	863	3.4	365	1.1	1,228	2.1	23	0.4	18,621
		その他	1,218	4.8	730	2.2	1,948	3.3	8	0.1	98,247
		その他県内小計	3,446	13.5	7,514	22.8	10,960	18.7	168	2.7	380,470
	福井県　計		24,686	96.5	27,172	82.3	51,858	88.5	6,179	99.6	762,654
県外	県外	石川県	852	3.3	730	2.2	1,582	2.7	9	0.1	―
		岐阜県	0	0.0	2,172	6.6	2,172	3.7	1	0.0	―
		その他	51	0.2	2,925	8.9	2,976	5.1	16	0.3	―
	県外小計		903	3.5	5,827	17.7	6,730	11.5	26	0.4	-
合　計			25,589	100.0	32,999	100.0	58,588	100.0	6,205	100	―

あ わ ら 病 院 組 織 図

令和７年４月１日現在



診療部

１．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
院長（循環器内科）	見附　保彦	日本内科学会 認定医・総合内科専門医・指導医 日本循環器学会　循環器専門医 福井大学 臨床教授 福井大学 不整脈・心不全先端医療講座 客員教授 日本内科学会　北陸地方会評議員 日本循環器学会　北陸地方会評議員
診療部長（小児科）	川満　徹	
神経内科医長	桐場　千代	日本内科学会　認定医 日本プライマリ・ケア連合学会　認定医・指導医 日本病院総合診療医学会　認定医 日本専門医機構 総合診療専門医研修 特任指導医
老年内科医師	栗田　敦	日本プライマリ・ケア連合学会　認定医・指導医 日本病院総合診療医学会　認定医
血液・腫瘍内科医長	大槻　希美	日本内科学会　認定医・総合内科専門医・指導医 日本血液学会　血液専門医・指導医 福井大学　臨床教授
内科医師	伊藤　和広	日本内科学会　認定医・総合内科専門医 日本血液学会　血液専門医・指導医 日本化学療法学会　抗菌化学療法認定医 日本感染症学会　感染症専門医 福井大学　臨床准教授
小児科医長	大坂　陽子	
内科医師	田中　周	

２．【部門の概要】

１）総合内科

当院の総合内科は、循環器内科、リウマチ科、血液・腫瘍内科、老年内科、神経内科といった専門診療科と連携しながら、幅広い内科疾患に対応しています。地域の診療所や医療機関との連携を密に図り、急性期から慢性期、在宅療養支援まで切れ目のない医療を提供しています。複数の疾患を併せ持つ高齢患者や診断が困難な症例にも対応し、地域医療の中核として総合的な診療を行っています。

２）循環器内科

虚血性心疾患、不整脈、心不全、大動脈疾患、肺高血圧症、末梢動脈疾患などの循環器疾患を中心に診療を行っています。病態に応じて安静時心電図、運動負荷心電図、24 時間ホルター心電図、脈波検査、心臓超音波検査、CT・MRI 検査などを実施し、疾患の早期発見と適切な治療に努めています。また、福井県内外の基幹病院と緊密に連携し、専門的治療や高度医療が必要な患者の紹介・逆紹介を円滑に行っています。

３）リウマチ科

関節リウマチ、リウマチ性多発筋痛症などのリウマチ性疾患をはじめ、全身性エリテマトーデス、シェーグレン症候群などの膠原病、ベーチェット病、全身性アミロイドーシス、痛風などの結晶誘発性関節炎、不明熱の診断・治療を行っています。関節超音波検査、サーモグラフィー、偏光顕微鏡検査、CT・MRI 検査などを迅速に実施できる体制を整えています。また、理学療法士・作業療法士によるリハビリテーション、薬剤師による服薬指導、臨床心理士による心理的支援など、多職種が連携しながら包括的な診療を提供しています。

４）血液・腫瘍内科

悪性リンパ腫、多発性骨髄腫、骨髄異形成症候群、慢性骨髄性白血病、慢性リンパ性白血病などの血液悪性疾患をはじめ、骨髄増殖性腫瘍や各種血液疾患の診療を行っています。急性白血病については専門施設と連携し、速やかな紹介を行っています。無菌管理を必要とする化学療法にも対応し、治療中の感染症や発熱などの合併症管理にも取り組んでいます。また、診断時から緩和ケアを並行して実施し、患者・家族の身体的・精神的負担の軽減に努めています。終末期医療においても、その人らしい療養生活を支援できるよう、多職種による包括的なケアを提供しています。

５）老年内科

高齢者に特有の疾患や症候群を対象に、急性期から慢性期、在宅療養支援まで幅広く診療を行っています。外来および一般病棟では肺炎などの感染症、認知症、嚥下障害を中心に診療し、障害者病棟では高度意識障害患者の長期療養支援にも取り組んでいます。また、地域の診療所や介護施設と連携し、特別養護老人ホームへの訪問診療支援や、通院困難な高齢者・障害者に対する訪問診療を実施しています。住み慣れた地域で安心して療養を継続できるよう支援しています。

６）神経内科

パーキンソン病、筋萎縮性側索硬化症（ALS)、多系統萎縮症などの神経難病をはじめとする神経疾患の診療を行っています。障害者病棟を活用した長期療養やレスパイト入院の受け入れを通じて、患者・家族の在宅療養を支援しています。また、毎週火曜日・金曜日の午前に神経内科外来を開設し、地域の医療機関とも連携しながら継続的な診療を行っています。

７）小児科

当院の政策医療の柱である障がい児（者）医療を担い、てんかんをはじめとする神経疾患や発達障害の診療を中心に行っています。病棟入院患者や通園利用児への医療提供に加え、医療的ケア児や重症心身障害児（者）の長期的な健康管理にも取り組んでいます。外来診療では神経疾患や発達障害に加え、感冒、肺炎、胃腸炎などの一般小児疾患にも対応しています。また、乳幼児健診や各種予防接種も実施し、地域の小児医療の充実に努めています。

３．学術活動

1）論文

Itoh K, Maruno D, Otsuki N, Tsutani H, Mitsuke Y, Iwasaki H

Paecilomyces variotii isolated from the blood of a patient with rheumatoid arthritis-related interstitial pneumonia
Int J Infect Dis　2025 Jun:155:107899.

Itoh K, Otsuki N, Suzuki Y, Kiriba C, Kuwata A, Tsutani H, Iwasaki H, Mitsuke Y
Successful Reswitching of Thrombopoietin Receptor Agonists: Two Cases of Immune Thrombocytopenia and Severe Aplastic Anemia
Intern Med　2025 Dec 15;64(24):3553-3556.

Itoh K, Tsutani H, Mitsuke Y, Ikawa M, Iwasaki H
Potential strategies for combination therapy involving medicines with differential signal transduction regulation effects and the mechanism of action of minocycline in septic neuroinflammation
Front Pharmacol　2025 Oct 9:16:1691613.

Itoh K, Tsutani H, Otsuki N, Kuwata A, Kiriba C, Urasaki Y, Ikawa M, Iwasaki H, Mitsuke Y
Anti-citrullinated Protein Antibody-positive Arthralgia Associated with an L110P-E148Q Double Heterozygoute: A Case-based Review
Internal Medicine　2026 Feb 1.

Itoh K, Tsutani H, Mitsuke Y, Ikawa M, Iwasaki H
A new therapeutic strategy for spotted fever group rickettsioses: a proposal for evaluating combination therapy with tetracycline and fluoroquinolones
Frontiers in Cellular and Infection Microbiology　2026 Mar 24:16:1798936.

2）学会発表

（国際学会）
27th Asia-Pacific League of Associations for Rheumatology Congress　2025/9/9　Fukuoka
The usefulness of the monocyte CD64/neutrophil CD64 ratio in autoimmune and autoinflammatory diseases: A single-center retrospective observational study
Itoh K, Otsuki N, Kuwata A, Kiriba C, Tsutani H, Ikawa M, Iwasaki H, Mitsuke Y

The 20th Asia Pacific Congress of Clinical Microbiology and Infection　2025/11/13　Bangkok
Evaluation of the Effect of Tetracycline and Fluoroquinolone Combination Therapy for Japanese Spotted Fever: A Comprehensive Analysis of Case Reports and Case Series
Itoh K, Kabata D, Shigemi H, Tsutani H, Mitsuke Y, Ikawa M, Iwasaki H

（国内学会）
第 122 回日本内科学会総会・講演会　2025/4/19　大阪
当院で経験した血液凝固第 XIII 因子欠乏症の後方視的検討
桐場千代，見附保彦，栗田 敦，大槻希美，伊藤和広，津谷 寛

第 87 回日本血液学会学術集会　2025/9/6　神戸
Carfilzomib 投与により血栓性微小血管症を認めた多発性骨髄腫
田中 周，伊藤和広，大槻希美，栗田 敦，桐場千代，浦崎芳正，津谷 寛，井川正道，岩﨑博道，見附保彦

第 79 回国立病院総合医学会　2025/11/7　金沢
HFpEF 合併高齢者 2 型糖尿病症例における DPP-4 阻害薬テネグリプチンの 心機能および動脈硬化指標に対する影響の後方視的検
桐場千代，見附保彦，栗田 敦，大槻希美，伊藤和広，田中 周，丸野大輝，角谷勇実，松下朋弘，宮本眞也，山下裕介，中山美智惠，南山啓吾

第 79 回国立病院総合医学会　2025/11/7　金沢
直接作用型抗凝固剤登場前後における当院後期高齢者非弁膜症性心房細動に 対するワルファリン治療の後ろ向き評価
桐場千代，見附保彦，栗田 敦，大槻希美，伊藤和広，田中 周，丸野大輝，角谷勇実，松下朋弘，宮本眞也，山下裕介，中山美智惠，南山啓吾

第 79 回国立病院総合医学会　2025/11/7　金沢
超高齢者慢性心不全症例におけるヒスタミン H1 拮抗薬による補正 QT 間隔 変動の後方視的検討
栗田 敦，桐場千代，大槻希美，伊藤和広，田中 周，浦崎正芳，津谷 寛，見附保彦

第 79 回国立病院総合医学会　2025/11/7　金沢
高尿酸血症患者における過剰一日尿酸排泄量の推算
栗田 敦，桐場千代，大槻希美，伊藤和広，田中 周，浦崎正芳，津谷 寛，見附保彦

第 79 回国立病院総合医学会　2025/11/7　金沢
Drug-induced thrombotic microangiopathy developed after the administration of carfilzomib in multiple myeloma
田中 周，伊藤和広，大槻希美，栗田 敦，桐場千代，津谷 寛，井川正道，岩﨑博道，見附保彦

第 79 回国立病院総合医学会　2025/11/8　金沢
自己免疫疾患および自己炎症性疾患における単球 CD64/好中球 CD64 比の有用性：後方視的観察研究伊藤和広，津谷 寛，大槻希美，栗田 敦，桐場千代，田中 周，井川正道，岩﨑博道，見附保彦

第 59 回日本痛風・尿酸核酸学会総会 2026/2/28　福井
HFpEF を合併した後期高齢 2 型糖尿病患者における DPP-4 阻害薬の血清尿酸値への影響：後方視検討
見附保彦，大槻希美，津谷 寛

第 59 回日本痛風・尿酸核酸学会総会 2026/2/28　福井
食塩摂取量と尿酸排泄量・排泄能との関連性
大槻希美，津谷 寛，見附保彦

薬剤科

1. スタッフ

役　　職	氏　　名	資格(専門医・認定医など)
薬剤科長	南山　啓吾	認定実務実習指導薬剤師
調剤主任	中山　実智恵	認定実務実習指導薬剤師、NST 専門療法士
薬剤師	山下　裕介	
薬剤師	林　優成	

2. 部門の概要

薬剤管理指導業務の積極的な実施100件/月、後発医薬品の採用促進、期限切れ医薬品の更なる削減、調剤過誤防止、ポリファーマシー改善への積極的な介入、医薬品情報発信の充実、研修会への積極的な参加、保険調剤薬局との連携、薬剤業務の効率化の実施

3. 業務実績

・薬剤管理指導料		1,530 件／年(前年度比 1.26 倍　前年度 1,210 件/年)
・無菌製剤処理料1	(抗がん剤)	169 件／年(前年度比 1.02 倍　前年度　165 件/年)
・無菌製剤処理料2	(TPN)	716 件／年(前年度比 0.86 倍　前年度　830 件/年)
・抗リウマチ薬の調製		131 件／年(前年度比 1.60 倍　前年度　113 件/年)

4. 学術活動実績

なし

放射線科

1．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
診療放射線技師長	宮本　眞也	ガンマ線透過写真撮影作業主任者 エックス線作業主任者
撮影透視主任	松下　朋弘	第１種放射線取扱主任者 Ｘ線 CT 認定技師 肺がん CT 認定技師
診療放射線技師	吉川　咲希	

2．部門の概要

■特色、運営方針

放射線科は３人と少人数ですが

・CT、MRI、TV、X 線検査などの高度な画像診断を行い迅速かつ正確な診断のサポートを行っています

・知識、経験を活かし STAT 画像の場合、直ちに医師に連絡をする体制を確立しています

・MRI の更新に伴い VSRAD が出来るようになりました

・患者さまの安全と快適さを最優先に考え、丁寧なサポートを心掛けています

・勉強会やセミナーへの積極的な参加をしています

・３６５日２４時間体制で診療に貢献しています

・患者様には明るく、優しく、正確にと柔軟に対応

・コミュニケーションスキルのレベルアップ

・各撮影室、廊下、待合室の環境整備

■機器設備

・一般撮影装置　１台　　X 線 TV 装置　１台　CT 装置（６４列）　１台　MRI 装置（0.3T）　１台

・ポータブル装置　２台　C アーム　１台　骨密度測定装置（超音波）　１台　画像処理装置　１台

3．業務実績

・直接撮影	2,358 件／年
・透視検査	71 件／年
・CT 検査	1,080 件／年
・MRI 検査	177 件／年
・骨塩定量（超音波）	442 件／年
・回診ポータブル	931 件／年
・画像取り込み・作成件数	245 件／年

検査科

1．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
臨床検査科技師長	角谷　勇実	認定輸血検査技師
医科学主任	丸野　大輝	超音波検査士（消化器）
臨床検査技師	深澤　里奈	
臨床検査技師	萬田　望	
臨床検査技師	中嶋　秀行	超音波検査士（消化器）、血管診療技師、細胞検査士、特定化学物質作業主任者
臨床検査技師	櫻田　浩美	
非常勤職員	西野　悠子	

2.部門の概要

- 採取した血液・尿などの主要検査については、迅速な結果報告を行い、診察前検査に対応しています。
- 生理機能検査では、超音波検査をはじめ、生活習慣病と密接に関連する血管検査に力を入れています。
- 早出シフトによる分析装置の立ち上げと病棟検体の回収を実施し、入院患者の検査結果を外来診察前に報告しています。また、分析装置の稼働が外来患者検体と重複しないよう調整し、外来検査の報告時間短縮に努めています。
- 緊急報告値については、「臨床検査のガイドライン JSLM2015」に基づき対応するとともに、必要に応じて担当者の判断により依頼医へ直接連絡し、その内容を記録しています。
- 検体検査の内部精度管理では、管理試料の測定および機器メンテナンスを実施し、測定結果の妥当性を確認しています。
- 外部精度管理では、日本医師会、日本臨床衛生検査技師会の精度管理調査ならびに各種メーカーサーベイに参加し、結果の検証と担当者間での情報共有、記録管理を行っています。
- 臨床検査委員会（月 1 回）および輸血療法委員会（月 2 回）を開催し、各診療科や病棟を通じて、医師をはじめとする多職種との連携・情報共有に取り組んでいます。
- 検査機器測定マニュアルおよび生理機能検査マニュアルに基づいた職員教育を実施するとともに、各種研修会や勉強会を通じて人材育成を推進しています。
- 研究活動として、フローサイトメーターを用いた CD64 抗原および CD25 抗原の測定を行い、炎症が感染性か非感染性かを判定するための検討に取り組んでいます。
- 検体検査部門では FMS 運用を導入しており、今後はさらなる自主運営体制の構築についても検討を進めています。

■施設基準：　・検体検査管理加算（Ⅱ）
・外来迅速検体検査加算
・感染対策向上加算 2
・輸血管理料Ⅱ
・輸血適正使用加算Ⅱ

■導入機器

検体検査部門

生化学：日立 7180
免疫：Sysmex　HISCL-800
血算：Sysmex　XB-100
凝固：Sysmex　CA-600
尿定性：SIEMENS　CLINTEK Advantus
血液ガス：RADIOMETER　ABL90FLEX
NH3：FUJIFILM　NH3-WⅡ
プロカルシトニン：SEKISUI　RapidPIAⅡ
フローサイトメーター：BECKMAN　COULTER DxFLEX
PCR 検査装置：TOSOH　TRC Ready-80

生理機能部門

超音波診断装置：GE　Logiq　E10s
超音波診断装置：FUJIFILUM　ARIETTA65、CANON　Aplio Air
多機能心電計：フクダ電子　FCP8300
ホルター解析機能付心電計：フクダ電子　FCP-8800
24 時間血圧計付ホルター心電図：フクダ電子 FM-200
血圧脈波検査装置：フクダ電子　Vasera　VS1500ATE
24 時間血圧計：フクダ電子　1F-250、FB-250
脳波計：日本光電
肺機能検査：フクダ電子　多機能電子スパイロメーター　SP-770)
聴力検査：リオン　AA77
痛み度：PainVision　PS-2100

3．業務実績

	項　　目	院内検査件数 総件数	外部委託検査件数
検体検査	**合計**	**136,475**	**7,779**
	尿・便検査	3,991	0
	髄液・精液等	9	0
	血液学的検査	13,454	34
	生化学的検査	109,146	1,852
	内分泌学的検査	1,492	173
	免疫学的検査	7,069	1,729
	微生物学的検査	1,314	3,879
	病理組織学的検査	0	33
	病理細胞学的検査	0	40
	機能検査	0	0
	染色体検査	0	15
	遺伝子検査	0	24
生理機能検査	**合計**	**2,797**	
	心電図検査等	1,073	
	脳波検査等	115	
	呼吸機能検査等	60	
	前庭・聴力機能検査等	63	
	眼科関連機能検査等	0	
	超音波検査等	1,476	
	その他	10	
穿刺・採取料等		2,575	

4．学術活動

第 79 回国立病院総合医学会　2025 年 11 月；石川県

丸野　大輝

「関節リウマチに伴う間質性肺疾患患者の血液から分離された Paecilomyces　Variotii」

リハビリテーション科

1．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
理学療法士長	仲山　卓志	がんのリハビリテーション研修終了 臨床実習指導者講習会終了 福祉住環境コーディネーター
主任理学療法士	田﨑　尚孝	がんのリハビリテーション研修終了 臨床実習指導者講習会終了
理学療法士	山口　まゆみ	介護支援専門員 福祉住環境コーディネーター
理学療法士	木津　実寿栄 （6 月末退職）	がんのリハビリテーション研修終了 臨床実習指導者講習会終了
理学療法士	平﨑　僚一	日本理学療法士協会認定理学療法士（運動器） がんのリハビリテーション研修終了 臨床実習指導者講習会終了
理学療法士	仲村　大地	臨床実習指導者講習会終了
理学療法士	松浦　多希	
主任作業療法士	洲崎　敏広	がんのリハビリテーション研修終了 臨床実習指導者講習会終了 福祉住環境コーディネーター
主任作業療法士	荒川　博志	がんのリハビリテーション研修終了 臨床実習指導者講習会終了
作業療法士	小林　純也	臨床実習指導者講習会終了
作業療法士	増山　千穂	
言語聴覚士	加藤　浩子	がんのリハビリテーション研修終了
言語聴覚士	児玉　純代	
理学療法補助員	山﨑　明子	

２．部門の概要

・政策医療（セーフティーネット）のうち、重症心身障がい児者、神経筋疾患への医療提供を柱に、その他各種疾患の急性期から維持期に効果的に介入し、質の高い理学療法、作業療法、言語聴覚療法を提供しています

・NST、褥瘡対策チーム等のチーム医療に参加し安全で高度な医療の提供に努めています

・各科・病棟カンファレンスを通じて医師や多職種との連携や情報共有に取り組んでいます

・新人教育マニュアルに則った職員教育をはじめ、各種研修会や勉強会を通じた人材育成を実践しています

・施設基準　：　脳血管疾患等リハビリテーション料（Ⅰ）
廃用症候群リハビリテーション料（Ⅰ）
運動器リハビリテーション料（Ⅰ）
呼吸器リハビリテーション料（Ⅰ）
障害児（者）リハビリテーション料
がん患者リハビリテーション料
摂食機能療法

■業務の内容

理学療法

・重症心身障がい児者、神経筋疾患、その他各種疾患の急性期から維持期の支援
（基本的動作練習、ADL、QOL 維持向上の取り組み、補装具の作製）

作業療法

・重症心身障がい児者、神経筋疾患、その他各種疾患の急性期から維持期の支援
（日常生活動作練習、環境整備、装具・自助具の作製、意思伝達装置を含めたコミュニケーション）

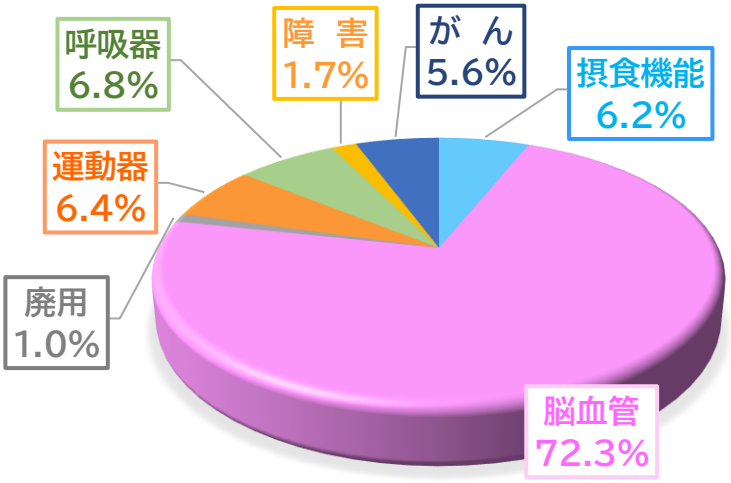
言語聴覚療法

・重症心身障がい児者、神経筋疾患、その他各種疾患の急性期から維持期の支援
（摂食、コミュニケーション）

３．業務実績

■年度間実施単位数

・脳血管リハ料：28,340 単位
・廃用症候群リハ料：392 単位
・運動器リハ料：2,526 単位
・呼吸器リハ料：2,674 単位
・障害児（者）リハ料：665 単位
・がん患者リハ料：2,209 単位
・摂食機能療法：2,395 件



栄養管理室

1.スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
栄養管理室長	宮城　正和	NST 専門療法士
主任栄養士	松本　楓子	日本病態栄養学会認定　NST 研修受講
非常勤事務助手	酒井　紀子	

2.部門の概要

栄養管理室では、安心・安全な食事を提供するため、衛生管理を徹底しながら、四季折々の食材を取り入れた行事食の提供、嚥下機能障害に配慮した形態調整食の提供などの給食管理業務を行っています。

また、栄養管理業務では、糖尿病や高血圧などの生活習慣病に対する栄養食事指導や、栄養サポートチームの一員として、医師、看護師、薬剤師など多職種と連携し、栄養管理計画の立案や喫食量のフォローを行っています。また、患者様が当院から施設や在宅へ移行されてからも、切れ目のない栄養管理が実践されるように、当院入院中の栄養管理に係る情報を記載した栄養情報提供書の作成も積極的に行っています。

3.業務実績

・栄養食事指導件数	434 件/年	（入院 32 件　外来 402 件）
・栄養サポートチーム加算	89 件/年	
・栄養情報連携料	39 件/年	

4.学術活動

特記事項なし

臨床工学室

1．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
主任臨床工学技士	藤嵜　孝次	臨床工学技士免許 臨床工学技士の業務範囲追加に伴う 厚生労働大臣指定による研修の履修

2．部門の概要

当院では、慢性期人工呼吸器管理を中心とした生命維持装置の設定・点検・トラブル対応を担い、モニタ関連装置やポンプ類などの医療機器の依存度の高い患者に対し、安全な医療提供を技術面から支えている。また、医師・看護師からの医療機器に対する技術的相談への対応を通じ、多職種が安心して診療・看護に専念できる体制づくりに寄与している。

3．業務実績

■人工呼吸器関連　1094 件

主な内訳：	人工呼吸器回路交換	314 件
	呼吸器フィルター交換	194 件
	時刻合わせ	220 件
	その他（人工呼吸器のオーバーホール、排痰補助装置の操作、加温加湿器の設定、トラブル対応、レスパイト対応、気管切開カニューレ相談、指示書作成、患者搬送など）	366 件

■ME 機器関連　391 件

主な内訳：	輸液・シリンジ・経腸ポンプ関連	61 件
	セントラルモニタ・送信機。ベッドサイドモニタ	141 件
	モニタ時刻合わせ	104 件
	その他	85 件

■その他　322 件

各種会議・各種カンファレンス・資料作成・メーカー対応など

4．学術活動

藤嵜孝次　臨床工学技士のものづくり～CE と企業を、モノをつなぐ～　第 11 回国立病院機構臨床工学技士協議会　2025 年 6 月 8 日：大分

藤嵜孝次　振動式ネブライザーを長期間使用したのちの加温加湿器内の水の性状について　第 47 回日本呼吸療法医学会　2025 年 8 月 30 日：大阪

藤嵜孝次　SpO2 監視システムのアラーム内容と傾向について　第 12 回筋ジストロフィー医療研究会学術集会　2025 年 10 月 25 日：長野

藤嵜孝次　佐藤和代　大坂陽子　川満　徹　人工呼吸器を装着した VATER 症候群患者の安全な入浴を目指して　第 79 回国立病院機構総合医学会　2025 年 11 月 8 日：石川

療育指導室

1．スタッフ

役　　職	氏　　名	資格（専門医・認定医など）
児童指導員	東　　優美	介護福祉士、サービス管理責任者、相談支援専門員 医療的ケア児等コーディネーター
児童指導員	小林　真理	社会福祉士、サービス管理責任者、相談支援専門員 医療的ケア児等コーディネーター
保　育　士	林　　美馨	保育士、介護福祉士、サービス管理責任者
保　育　士	松浦いづみ	保育士、介護福祉士、サービス管理責任者、 相談支援専門員、医療的ケア児等コーディネーター
保　育　士	宮川　朋和	保育士、介護福祉士、サービス管理責任者
保　育　士	三枝　　裕	保育士、ヘルパー２級、サービス管理責任者
保　育　士	上出　眞紀	保育士
保　育　士	一　　里美	保育士
保育助手	牧野　聡子	教員免許（音楽）

2．部門の概要

入所事業（療養介護・医療型障害児）、通所事業（生活介護・児童発達支援・放課後等デイサービス・居宅訪問型児童発達支援）、相談支援事業（当院療養介護利用者のみ）、重症心身障害児者・医療的ケア児者への障害福祉サービス全てに携わり、地域協議会では事務局を担ったりと地域ニーズに寄り添ったサービス提供を行っている。

生活支援では全利用者様の障害特性や年齢、趣味・趣向に合わせた目標を立て、集団活動・個別援助・小グループ活動・行事を実施し、利用者様の生活の中に楽しみ・生きがいを提供できるよう支援している。

3．業務実績

・入所利用者数：９０名（療養介護：８４名、医療型障害児入所：５名、措置入所：１名）
・短期入所・日中一時支援　登録者数：２１名
　R７年度実績１１８名：３６４日利用　新規利用開始：４名
・通所事業（生活介護・児童発達支援・放課後等デイサービス・居宅訪問型児童発達支援）
　登録者数：生活介護１２人、児童発達支援３人、放課後等デイサービス１人、

居宅訪問型児童発達支援１人　　１日受け入れ平均　４．５８人

・相談支援　新規作成：２０件　モニタリング：(年２回）１４２件　相談支援事業利用者：８６名

・相談支援　新規作成：２０件　モニタリング：(年２回）１４２件　相談支援事業利用者：８４名

４．学術活動

・国立病院機構総合医学会

保育士　　林　美馨　「重心病棟５０周年記念イベント　　～療育指導室としての関わり～」

心理療法室

1. スタッフ

役　　職	氏　　名	資格(専門医・認定医など)
心理療法士	石田　悠	臨床心理士・公認心理師

2. 部門の概要

【外　来】

小児科部門では、主に発達の気がかりさを持つ就学前の幼児から中学生までの心理・発達検査および療育を実施している。また、様々な理由で登校しぶりや不登校、引きこもり傾向にある就学後から高校生までの心理カウンセリングも行っている。教育・福祉・行政といった関係機関・施設との情報共有も定期的に実施している。また、発達障害児に対して薬物治療の必要性がある場合には他の医療機関への紹介も検討・実施・連携を図っている。

リウマチ科、血液・腫瘍内科部門では、疾患によりうつ傾向にある患者様や患者様を支えるご家族に対して、生活環境がよりよいものになることを目指したアプローチを軸とし、心理療法を実施している。【院　内】

小児科、神経内科、血液・腫瘍内科部門において療養・入院生活を送られている患者様に対する心理療法を中心とした関わりを実施している。認知症、うつ病といった精神疾患のスクリーニングを目的とした依頼を受けて各種心理検査を実施する場合もある。

3. 業務実績

■小児科　新規 6件 ・ 継続 15件
（内 訳）各種心理検査 16件 / 心理療育 15件 / 心理療法 2件

■循環器科　新規 1件 ・ 継続 0件　（内 訳）各種心理検査 1件

■血液・腫瘍内科　新規 3件 ・ 継続 1件
（内 訳）各種心理検査 2件 / 心理療法 3件

■リウマチ科　新規 0件 ・ 継続 3件 （内 訳）心理療法 3件

■神経内科　新規 0件 ・ 継続 3件 （内 訳）各種心理検査 2件 / 心理療法 3件

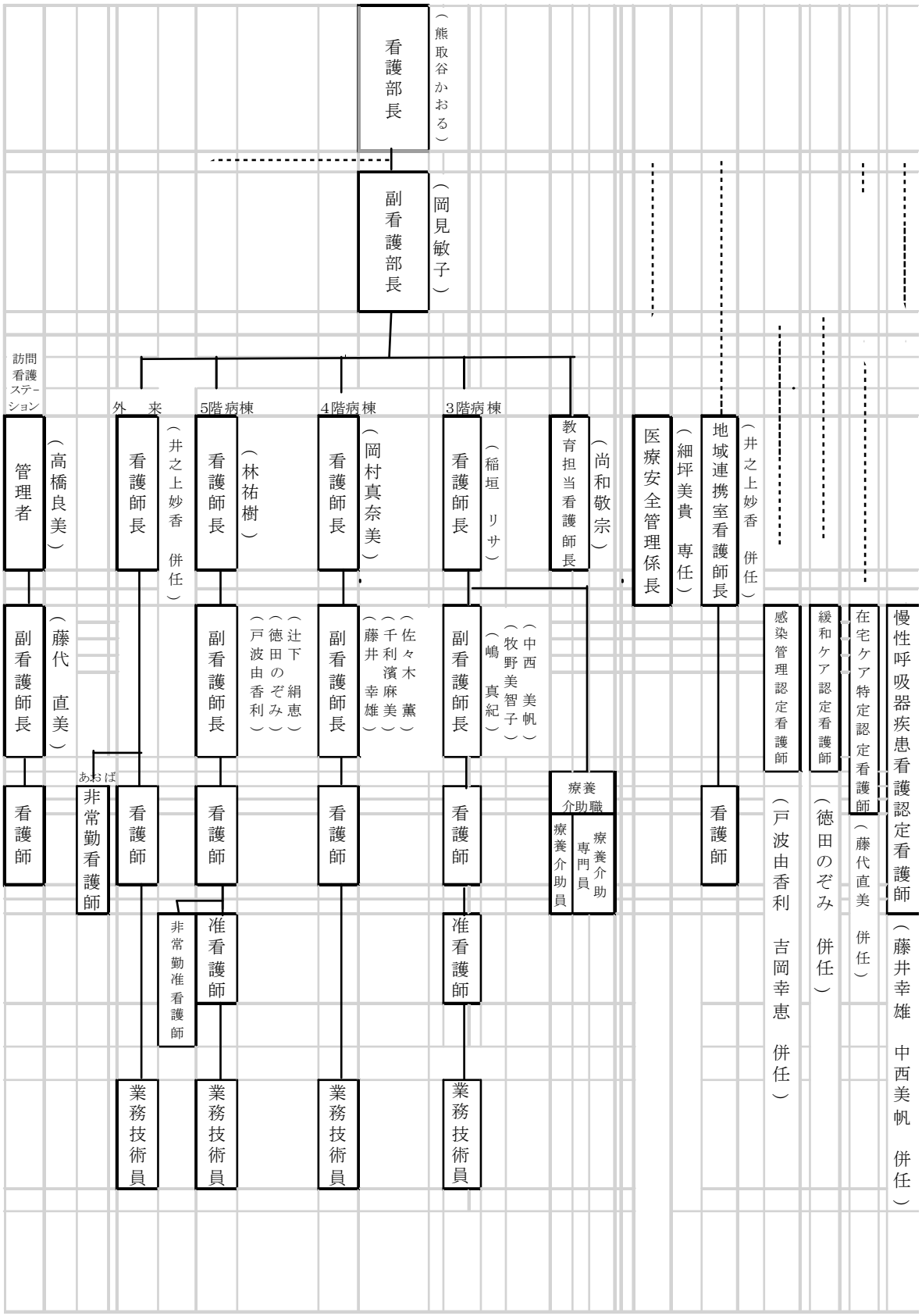
■内 科　新規 1件 ・ 継続 1件 （内 訳）各種心理検査 1件 / 心理療法 1件

■その他　会議・カンファレンス対応など　15件

4. 学術活動：未参加

看護部

Ⅰ．組織図


看護部長（熊取谷かおる）
副看護部長（岡見敏子）
訪問看護ステーション
外来
5階病棟
4階病棟
3階病棟
教育担当看護師長（尚和敬宗）
医療安全管理係長（細坪美貴 専任）
地域連携室看護師長（井之上妙香 併任）
感染管理認定看護師（戸波由香利 吉岡幸恵 併任）
緩和ケア認定看護師（徳田のぞみ 併任）
在宅ケア特定認定看護師（藤代直美 併任）
慢性呼吸器疾患看護認定看護師（藤井幸雄 中西美帆 併任）
管理者（高橋良美）
看護師長（井之上妙香 併任）
看護師長（林祐樹）
看護師長（岡村真奈美）
看護師長（稲垣 リサ）
副看護師長（藤代 直美）
副看護師長（辻下 絹恵）（徳田のぞみ）（戸波由香利）
副看護師長（佐々木 薫）（千利濱麻美）（藤井 幸雄）
副看護師長（中西 美帆）（牧野美智子）（嶋 真紀）
看護師
あおば
非常勤看護師
看護師
看護師
看護師
看護師
療養介助職
療養介助員
療養介助専門員
看護師
非常勤准看護師
准看護師
准看護師
業務技術員
業務技術員
業務技術員
業務技術員

Ⅱ．運営方針

看護部の理念

地域の保健医療ニーズに対応し、皆さまの意思と人権を尊重し、生命と健康を守り、こころ安らぐ温かい看護を提供します

《看護の方針》

1.根拠に基づく安全で確かな看護を実践します
2.寧で分かりやすい説明を行い、患者さまの意思を尊重し満足いただける看護を提供します
3.安全管理に関する取り組みを強化します
4.専門医療を推進できる人材を育成します
5.効率的で自立した病院経営に参画します

Ⅲ．令和 7 年度　看護部目標

丁寧で温かい看護の提供を基本として、地域に貢献する組織を創る

【経営の安定】

病院経営への参画

1　患者確保（入院患者数・外来患者数・訪問看護利用者の確保）
地域、施設との交流、連携強化
柔軟な病床管理
地域包括ケア病床の効率的な運用

【医療の質の向上】

看護の質向上

1．ﾁｰﾑ医療の推進
身体拘束最小化への取り組みの強化
倫理カンファレンス、多職種カンファレンス
チームカンファレンスの充実
退院前訪問、退院後訪問の強化

2．専門性の高い看護実践
看護研究の推進
重症心身障がい児（者)、難病患者の看護実践力の向上
認定看護師・特定行為看護師等、研修受講の推進
リソースナース（認定看護師、特定行為看護師）を活用した看護実践力の向上

【サービスの向上】

1．地域への情報発信
地域住民の健康増進に向けてのイベント開催
ブログ、インスタグラムを活用した地域への情報発信

2．患者・職員満足度向上への取り組み
虐待の目を積む組織文化の醸成
医療安全、感染管理の強化
療養環境の整備
やりがいのある職場風土の構築

時間外勤務の削減
年次休暇取得の推進

【管理】

1．人材確保と定着
働きやすい職場環境の醸成

2．業務改善の推進
看護提供方式の検討

3．キャリア開発
スペシャリスト・ジェネラリストの育成

Ⅳ．業務実績

1．院外研究発表

学会名	病棟名	発表者名	テーマ
第 67 回近畿看護学会 R6.9.7	4階病棟	岡村真奈美	骨折防止チームの効果的な活用に向けた取り組み ～コッターの変革理論を用いて～
第 79 回 国立病院総合医学会 R7～11.8	3 階病棟	森大起	重症心身障害児（者）病棟における横地分類の 移動機能レベルの違いによる外傷部位の比較
	4 階病棟	髙橋由香	重症心身障害児（者）病棟における看護師と療養介助職員のやりがいに影響する要因
	副看護師長会	佐々木　薫	Be Real ～地震発生時の初期対応への取り組み～
第15回日本在宅看護学会学術集会 R7.11.29	訪問看護ステーション	藤代直美	在宅療養を支える家族支援型特定行為 ー胃ろう管理を通した訪問看護の役割ー

第49回東海北陸神経筋ネットワーク研究会 R7.6.27	4階病棟	弓良静枝 岡村真奈美	閉じ込め状態となった筋萎縮性側索硬化症患者の看護を振り返って
第50回東海北陸神経筋ネットワーク研究会 R7.11.14	4階病棟	小林寛奈	非侵襲的陽圧換気療法を導入した ALS 患者の終末期看護を振り返って

2．講師派遣

研修会名等	病棟名	講師者名	内容
R7.6.28　感染管理 リーダー育成研修	4 階病棟	吉岡幸恵	施設における感染対策の課題について （問題抽出シートの記載など）
R7.7.28　福井大学　子どもの発達と障がい看護論	4 階病棟	菅原大樹	～重症心身障がい児の看護の実際～

R7.8.2 看護師の特定行為に関する研修	訪問看護ステーション	藤代直美	特定行為研修修了者の活動報告
R7.8.26 専門･認定看護師出前講座 ハートフル訪問看護ステーション	5 階病棟	徳田のぞみ	癌患者のリンパ浮腫ケアについて
R7.9.25 専門･認定看護師出前講座 坂井地区医師会ケアセンター	訪問看護ステーション	藤代直美	訪問看護での倫理的問題 コミュニケーションと接遇
R7.10.15 専門・認定看護師出前講座 新田塚訪問看護ステーション	5 階病棟	徳田のぞみ	リンパ浮腫ケアについて
R7.12.5 専門･認定看護師出前講座 安川病院	訪問看護ステーション	藤代直美	在宅に向けての支援･病院と訪問看護ステーションとの連携
R7.12.10 坂井地区在宅患者情報共有システム利用者向け研修会	訪問看護ステーション	藤代直美	カナミック「TRITRUS」活用事例の紹介
R8.2.21 看護師職能委員会ⅠⅡ合同研修会	訪問看護ステーション	藤代直美	特定行為看護師の地域活用と病院との連携～特定看護師の活躍と現状～

３．院外研修

研修名	主催	開催日	病棟名	参加者名
勤務時間管理研修	近畿グループ	R7.5.12	3 階病棟	稲垣リサ
医療安全対策研修Ⅱ	近畿グループ	R7.6.13	看護部長室	細坪美貴
教育担当看護師長研修	近畿グループ	R7.6.20	看護部長室	尚和敬宗
副看護師長研修	近畿グループ	R76.23	4 階病棟	千利濵麻美
新任中堅監督者研修	近畿グループ	R7.7.8 R7.11.13	3 階病棟	稲垣リサ
看護師長新任研修	近畿グループ	R7.7.14	3 階病棟	稲垣リサ
医療安全対策研修Ⅰ	近畿グループ	R7.9.5～R7.10.8 R7.10.23	4 階病棟	佐々木薫
保健師助産師看護師実習指導者講習会Ⅱ期	近畿グループ	R7.9.30～R7.12.5	4 階病棟	大島怜暢
中堅看護師長研修	近畿グループ	R7.9.11	4 階病棟	岡村真奈美

重症心身障害児（者）ケア研修	近畿グループ	R7.11.27	3 階病棟 4 階病棟	安藤実保 白畑里香
医療安全対策研修Ⅱ	近畿グループ	R7.12.8	看護部長室	細坪美貴
虐待防止対策研修（管理職者）	近畿グループ	R7.11.25	3 階病棟	稲垣リサ
障害者虐待防止対策研修（実務者）	近畿グループ	R8.1.23	3 階病棟 4 階病棟	森　大起 千利濵麻美
院内感染対策研修	近畿グループ	R8.3.5	5 階病棟	栗田由香利

研修名	主催	開催日	病棟名	参加者名
認知症ケア研修	国立病院機構本部	R7.6.17～R7.7.9 R7.2.23	3 階病棟 地域連携	嶋　真紀 奥野美貴
看護補助者の更なる活用のための看護管理研修	国立病院機構本部	R7.7.1～R7.7.24 R7.7.31	5 階病棟	林　祐樹
認知症ケア研修	国立病院機構本部	R7.12.10～R8.1.7 R8.1.21	5 階病棟	辻下絹恵
看護補助者の更なる活用のための看護管理研修	国立病院機構本部	R7.12.16～R8.1.14 R8.1.27	5 階病棟	佐々木薫
療養介護サービス研修	国立病院機構本部	R8.1.30	4 階病棟	岡村真奈美

研修名	主催	開催日	病棟名	参加者名
てんかん看護セミナー	国立病院機構 静岡てんかん・ 神経医療センター	R7.10.23～ R7.10.24	3 階病棟 4 階病棟	村上星里加 川上晴菜
てんかんに関する看護師研修会	国立病院機構 西新潟中央病院	R7.11.4～ R7.12.26	3 階病棟 4 階病棟	看護師 12 名

看護協会・そのほか

研修名	主催	開催日	病棟名	参加者名
NST 研修	福井大学医学部 附属病院	R7.5.28～R7.11.28	4 階病棟 5 階病棟	高橋由香 辻下絹恵
実習指導者研修	大阪医療センター 附属看護学校	R7.5.30 R7.6.27	訪問看護	若松千恵子
訪問看護師養成講習会	福井県看護協会	R7.6.4 ～R7.12.3 実習 3 日間	訪問看護	若松千恵子
実習指導者研修	京都医療センター 附属看護学校	R7.6.13 R7.7.14	3 階病棟 地域連携	村上星里加 福嶋志保子
感染管理リーダー育成研修	福井県看護協会	R7.6.28～11.25 6 日間	4 階病棟	吉田春奈

福井県ELNEC-Jコアカリキュラム看護師教育プログラム	福井県立病院	R7.9.27～R7.9.28	3階病棟 5階病棟	水口香織 村越加代
認定看護管理者教育課程 ファーストレベル	福井県看護協会	R7.9.26～R7.12.6	4階病棟	岡村真奈美
在宅現場における カスタマーハラスメント研修	福井県在宅医療 サポートセンター	R7.10.3	訪問看護	藤代直美
感染管理リーダー育成 フォローアップ研修	福井県看護協会	R7.10.4	3階病棟 4階病棟	森　大起 加藤朋江
福井大学メディカルラリー	福井大学医学部 附属病院	R7.11.3	3階病棟 4階病棟 5階病棟	酒井卓弥 道場ゆか理 辻下絹恵
先輩看護師と看護学生の 交流会	福井県看護協会 ナースセンター	R7.11.13 R7.11.28 R7.12.18	3階病棟 4階病棟 5階病棟	川﨑彩夢 木本妃奈 牧野美羽
HHSAF トレーニング・観察・評価方法について（施設見学）	大阪医療センター	R8.2.24	事務部長 内科医師 副看護師長	小西孝一 伊藤和広 栗田由香利

Ⅴ．実習受け入れ

令和7年	地域ケア実習	福井大学医学部看護学科	R7.6.9～ R7.11.28	47日	20名
	小児看護学実習	福井大学医学部看護学科	R7.6.9～R7.11.7	48日	30名
	在宅看護実習	福井工業大学附属福井高等学校	R7.6.23～R7.7.4	9日	2名
	小児看護学実習	福井工業大学附属福井高等学校	R7.10.14～ R7.10.31	14日	37名
	看護マネジメント実習	福井県立大学・看護学科	R7.6.3　R7.6.5 R7.7.8　R7.7.11	4日	4名

事務部

１．スタッフ

役　　職	氏　　名	役　　職	氏　　名
事務部長	小西　宏一	事務助手	下家　直子
業務班長	山本　真佐雄	事務助手	青池　淳子
庶務班長	星　　大輔	事務助手	幸川　宏美
医事専門職	是澤　勇	事務助手	石橋　眞奈美
契約係長	西村　重之	事務助手	田端　玲菜
庶務係長	杉本　翔平	事務助手	渡邊　加代美
医事係長	橋本　慎平	事務助手	眞垣　知代
一般職員	安達　峰子	事務助手	松下　美紅
一般職員	西出　実央	事務助手	高戸　愛香
一般職員	上田　宇意人	事務助手	斉藤　智美
一般職員	佐々木　映彰	事務助手	川邊　ゆう子
一般職員	前川　滉真	事務助手	田畑　美幸
一般職員	池田　和靖	事務助手	井上　由美子
医療社会事業専門員	新谷　裕子	事務助手	街道　洋子
		事務助手	細木　律男
		事務助手	小林　由紀雄
		事務助手	東村　卓受
		事務助手	五味　雅美

２．部門の概要

（２０２５年度事務部門の運営方針）

①経営目標の達成（事務部長）

・経常収支率１０３％の達成

➡ 診療報酬制度を活用した収益増化策の提案

➡ コストカットの推進（ＳＰＤ化導入の検討、一括購買・契約の検討）

②経営体質の強靭化

・ベンチマーク（他施設との比較）による、中期的な経営戦略の提案（事務部長）

➡ 施設基準　新基準・上位基準の取得、職員配置の見直し

・診療報酬対策の徹底（医事専門職）

➡ 算定漏・査定対策、未請求件数の減少

③専門医療の充実（庶務班長）

・診療体制見直しにおける事務的サポート体制の構築

④医療介護福祉専門教育の充実（庶務班長）

・教育体制充実にかかる事務的サポート体制の構築

⑤臨床研究の推進（業務班長）

・研究発表会への積極的な参加

⑥広報の充実（庶務班長）

・広報活動戦略の見直し

➡ ＳＮＳの積極的な活用

➡ 情報発信力を数値で検証し、費用対効果を追求する

⑦医療サービスの推進（業務班長）

・病院アメニティの改善、充実

・障害福祉サービス利用者のアウトリーチ推進

⑧職員満足度の充実（庶務班長）

・休暇取得日数の増加、職場環境の見直し

⑨業務の効率化（業務班長）

・最適な医療ＤＸの導入

➡ スマホ導入を想定した運用方法を検討する

⑩人材確保（庶務班長）

・職員確保体制の見直しと構築

・費用対効果を確認し、あらゆる媒体・関係機関を最大限活用する

⑪心理的安全性が保たれた職場風土の構築（事務部長）

・効率的に情報共有し、部門における課題把握・対策実施を徹底する

・職員アメニティーの改善、充実

・虐待防止の更なる推進（医事専門職）

⑫防災対策の整備（庶務班長）

・災害・消防訓練の実施に基づく、ＢＣＰ（事業継続計画）の見直し

臨床研究部

１．スタッフ

役　　職	氏　　名
臨床研究部長（併任）	見附　保彦
治験管理室長（併任）	南山　啓吾
治験管理事務長（併任）	山本　真佐雄
データーマネージャー	青池　淳子

２．部門の概要

国立病院機構設立の目的の一つとして臨床研究を行うことが規定されており、全国の国立病院機構病院には臨床研究センター・臨床研究部・院内標榜臨床研究部が設置されています。

このような取り組みを踏まえ、当院では平成 17 年度より臨床研究部を院内標榜し、当院の診療の柱である血液・免疫疾患、長寿・障がい者医療に関する臨床研究を主体とし、各疾患の病因の解明、診断、治療法の開発等、臨床ならびにその基礎となる研究を院内各部門と密接に連携し行っています。特に研究スピリットを有する職員を育てるために、毎年 1 回 6 月に「臨床研究実践キャンプ」を開催し、また毎週金曜日に「臨床研究相談」では研究計画の作成・指導を行っています。これらの臨床研究がもたらす結果が、日常的な医療行為の一つ一つとしっかり連結し、より質の高い医療を築いていきたいと考えています。

3. 業務実績

2025年度　研究業績一覧

No	課題名	研究代表者	所属
1	当院での高齢患者に対する漢方製剤荊芥連翹湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
2	当院での高齢患者に対する漢方製剤三黄瀉心湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
3	当院におけるスルピリド使用症例の安静時心電図におけるＱＴ時間についての検討	栗田　敦	医局
4	当院におけるエスシタロプラム使用症例の安静時心電図におけるＱＴ時間についての検討	栗田　敦	医局
5	当院におけるセルトラリン使用症例の安静時心電図におけるＱＴ時間についての検討	栗田　敦	医局
6	遷延性意識障害症例における唾液分泌コントロールを目的とした院内製剤スコポラミン軟膏の有用性について	桐場　千代	医局
7	NHO近畿グループにおけるプレアボイド報告の集積調査	南山　啓吾	薬剤科
8	当院での高齢患者に対する漢方製剤柴胡加竜骨牡蛎湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
9	当院での高齢患者に対する漢方製剤柴胡桂枝乾姜湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
10	当院での高齢患者に対する漢方製剤柴胡桂枝湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
11	当院での高齢患者に対する漢方製剤柴胡清肝湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
12	当院での高齢患者に対する漢方製剤柴朴湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
13	当院での高齢患者に対する漢方製剤柴苓湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
14	当院での高齢患者に対する漢方製剤潤腸湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
15	当院での高齢患者に対する漢方製剤女神散による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
16	当院での高齢患者に対する漢方製剤小柴胡湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
17	当院での高齢患者に対する漢方製剤小柴胡湯加桔梗石膏による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
18	当院での高齢患者に対する漢方製剤清上防風湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
19	当院での高齢患者に対する漢方製剤清心蓮子による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
20	当院での高齢患者に対する漢方製剤清肺湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局

21	当院での高齢患者に対する漢方製剤大柴胡湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
22	当院での高齢患者に対する漢方製剤二朮湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
23	WHO手指衛生自己評価フレームワーク（HHSAF）を用いた手指衛生剤使用量変化に関する有効性の評価	伊藤　和広	医局
24	医療ソーシャルワーカーにおける相互チェックの効果と有効な実施方法の検討 ―業務の質向上を中心とした効果の検証―	新谷　裕子	事務
25	当院での高齢患者に対する漢方製剤半夏瀉心湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
26	当院での高齢患者に対する漢方製剤防風通聖散による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
27	当院での高齢患者に対する漢方製剤竜胆瀉肝湯による薬剤性肝障害発症の後方視的検討	栗田　敦	医局
28	当院におけるイバブラジン使用症例の安静時心電図におけるＱＴ時間についての検討	桐場　千代	医局

課題 No. 23 および No. 24 を除きすべて終了（2026 年 7 月末）

Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5412-25
Intern Med Advance Publication
http://internmed.jp

【 CASE REPORT 】

Successful Reswitching of Thrombopoietin Receptor Agonists: Two Cases of Immune Thrombocytopenia and Severe Aplastic Anemia

Kazuhiro Itoh[1,2], Nozomi Otsuki[1], Yusuke Suzuki[1], Chiyo Kiriba[1], Atsushi Kuwata[1], Hiroshi Tsutani[1], Hiromichi Iwasaki[2] and Yasuhiko Mitsuke[1]

Abstract:
We used thrombopoietin receptor agonists (TPO-RAs) to treat immune thrombocytopenia (ITP) and aplastic anemia (AA). Molecular structures and methods of action differ among TPO-RAs; therefore, switching to another may be beneficial if one fails. In elderly people, planning and attending outpatient visits may complicate weekly subcutaneous romiplostim delivery. In two cases, the patient was initially unresponsive to eltrombopag, so we switched to romiplostim and then switched back due to hospital visits, which resulted in stabilizing platelet counts. We suggest better management techniques for patients, as ITP and AA require long-term management, which becomes increasingly challenging with increasing patient age.

Key words: aplastic anemia, eltrombopag, immune thrombocytopenia, romiplostim, thrombopoietin receptor agonist

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.5412-25)

Introduction

Immune thrombocytopenia (ITP) and aplastic anemia (AA) are autoimmune disorders that cause thrombocytopenia. Current guidelines indicate that, for ITP, if a patient fails to respond successfully to corticosteroid treatment as first-line therapy, thrombopoietin receptor agonists (TPO-RAs), rituximab, or splenectomy are viable second-line therapy options (1). The combination of a TPO-RA and immunosuppressive therapy is known to enhance the response rate of elderly AA patients ineligible for allogeneic hematopoietic stem cell transplantation (2, 3). TPO-RAs are effective against severe AA unresponsive to the first immunosuppressive therapy and can treat three types of blood cells, including platelets (4).

In Japan, the available TPO-RAs for the treatment of these disorders are eltrombopag and romiplostim. These two TPO-RAs have distinct three-dimensional structures and different mechanisms of action. Eltrombopag interacts with the transmembrane domain of the TPO receptor, resulting in its activation (5). In contrast, romiplostim stimulates TPO-R by attaching to its extracellular domain (6). The strategy of switching to a different TPO-RA after the patient exhibits resistance to treatment has shown efficacy in both ITP and AA, even though different pathological mechanisms are involved (7, 8). Eltrombopag is an oral drug, whereas romiplostim is administered via weekly subcutaneous injection, which necessitates outpatient visits due to the prohibition of self-administration in Japan. In our clinical experience, the frequency of hospital visits can pose challenges to some patients, leading to compliance issues.

We herein report two cases of ITP and AA in which the patients became resistant to eltrombopag, switched to romiplostim, and then switched back to eltrombopag due to difficulties in hospital visits, ultimately achieving positive responses to treatment.

[1]Department of Internal Medicine, NHO Awara National Hospital, Japan and [2]Division of Infection Control and Prevention, University of Fukui Hospital, Japan
Received: February 2, 2025; Accepted: May 1, 2025; Advance Publication by J-STAGE: June 19, 2025
Correspondence to Dr. Kazuhiro Itoh, kitoh@u-fukui.ac.jp

Case Reports

Case 1

An 89-year-old woman had been diagnosed with ITP 5 years prior and was receiving eltrombopag at 25 mg/day. She was hospitalized after a fall that resulted in a fracture of the left femoral trochanter. She underwent osteosynthesis surgery; however, her platelet count decreased postoperatively. Consequently, the attending physician increased the eltrombopag dose to 37.5 mg/day, and prednisolone was added at 20 mg/day, but her condition did not improve, so she was transferred to our hospital (Day 1). At the time of transfer, the platelet count had decreased to 8×10^9/L, and 10 units of platelet transfusion were administered. Following the transfer, we increased the prednisolone dose to 40 mg/day and switched from eltrombopag to romiplostim at a dose of 1 μg/kg, gradually increasing to 10 μg/kg over a month. The platelet count increased to over 30×10^9/L, with a maximum recorded value of 152×10^9/L. On Day 149, the patient suffered a tumble, leading to fracture of the right femoral neck, and she subsequently underwent osteosynthesis again. However, continuous administration of romiplostim (with oral prednisolone) did not significantly lower her platelet count, enabling her to continue rehabilitation and leave the hospital. Subsequently, she expressed concerns about the difficulty of hospital visits. As a result, on Day 1,401, we switched romiplostim back to eltrombopag at 25 mg/day. Since then, the platelet count has stabilized at 30-100×10^9/L, and the patient has consistently improved without complications (FigureA).

Case 2

An 86-year-old woman with severe AA and paroxysmal nocturnal hemoglobinuria (PNH)-positive red blood cells (0.11% positivity on 2-color flow cytometry) (9) had experienced a fall approximately 1 month earlier. This incident resulted in a fracture of the left pubic bone, necessitating hospitalization. She was treated conservatively at the previous hospital and then transferred to our hospital for rehabilitation (Day 1). Following the diagnosis of AA, she underwent immunosuppressive therapy with cyclosporine, as the risk of adverse effects made anti-thymocyte globulin unsuitable. However, the treatment was ineffective. The attending physician recommended the administration of eltrombopag, but she declined this option because of concerns regarding possible side effects. Supportive therapy was therefore provided weekly, accompanied by 10 platelet transfusions, maintaining a platelet count of 10×10^9/L. Monthly transfusions of 2 units of red blood cells maintained a hemoglobin level of 7.0 g/dL. Her doctors prescribed rivastigmine and esomeprazole for comorbidities, such as Alzheimer's dementia and gastroesophageal reflux disease. Following hospitalization for a left pubic bone fracture, she consented to eltrombopag treatment. Administration of eltrombopag at 75 mg/day successfully maintained a platelet count of $\geq10\times10^9$/L without requiring blood transfusion. Following transfer to our hospital (after Day 1), we monitored the patient without performing red blood cell or platelet transfusion support therapy for AA, and the patient showed favorable recovery without complications. After discharge from the hospital, a decrease in the platelet count indicated diminished responsiveness to eltrombopag. Therefore, she was switched to romiplostim on day 144, with the dosage was increased from 10 to 20 μg/kg over a 3-month period. Subsequently, the platelet count increased to 10-30×10^9/L. However, the patient expressed concerns about the inconvenience associated with the frequency of hospital visits. As a result, we switched the treatment regimen back on Day 462, from romiplostim to eltrombopag at a daily dosage of 100 mg. The platelet count subsequently stabilized at 20-30×10^9/L without a notable decline, and the patient has been progressing well without complications (FigureB).

Discussion

We successfully switched to romiplostim for an ITP patient and thrombocytopenia for a patient with severe AA who had become unresponsive to eltrombopag. However, we encountered situations in which frequent hospital visits posed challenges owing to the advanced age of the patients, necessitating switching back to eltrombopag. To our knowledge, this report represents the first description of the successful reswitching of TPO-RAs for ITP and AA.

In relation to TPO-RA switching, the response rate has been reported to be 46% when switching from romiplostim to eltrombopag and 80% when switching from eltrombopag to romiplostim in ITP patients (7). Furthermore, in AA patients, the response rate for ≥1 blood cell type was 76%, while that for platelet count alone was 48%, following a switch from eltrombopag to romiplostim (8). As previously stated, eltrombopag and romiplostim have distinct molecular structures and mechanisms of action (5, 6). Furthermore, these drugs affect intracellular signaling pathways in different ways. For example, eltrombopag has a smaller impact on the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway than does romiplostim. However, both drugs activate the serine/threonine kinase (AKT) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways, with romiplostim activating the AKT and MAPK/ERK pathways to a lesser extent. In contrast, eltrombopag activates both pathways equally (10). The different stimulatory effects on megakaryocyte formation may be due to differences in the signal transduction cascades. In summary, romiplostim mainly increases the number of megakaryocytes, whereas eltrombopag aids megakaryocyte maturation and platelet precursor growth (10). These different mechanisms of action shed light on why patients resistant to one TPO-RA may respond to another.

The reasons for the refractoriness of TPO-RA remain in-

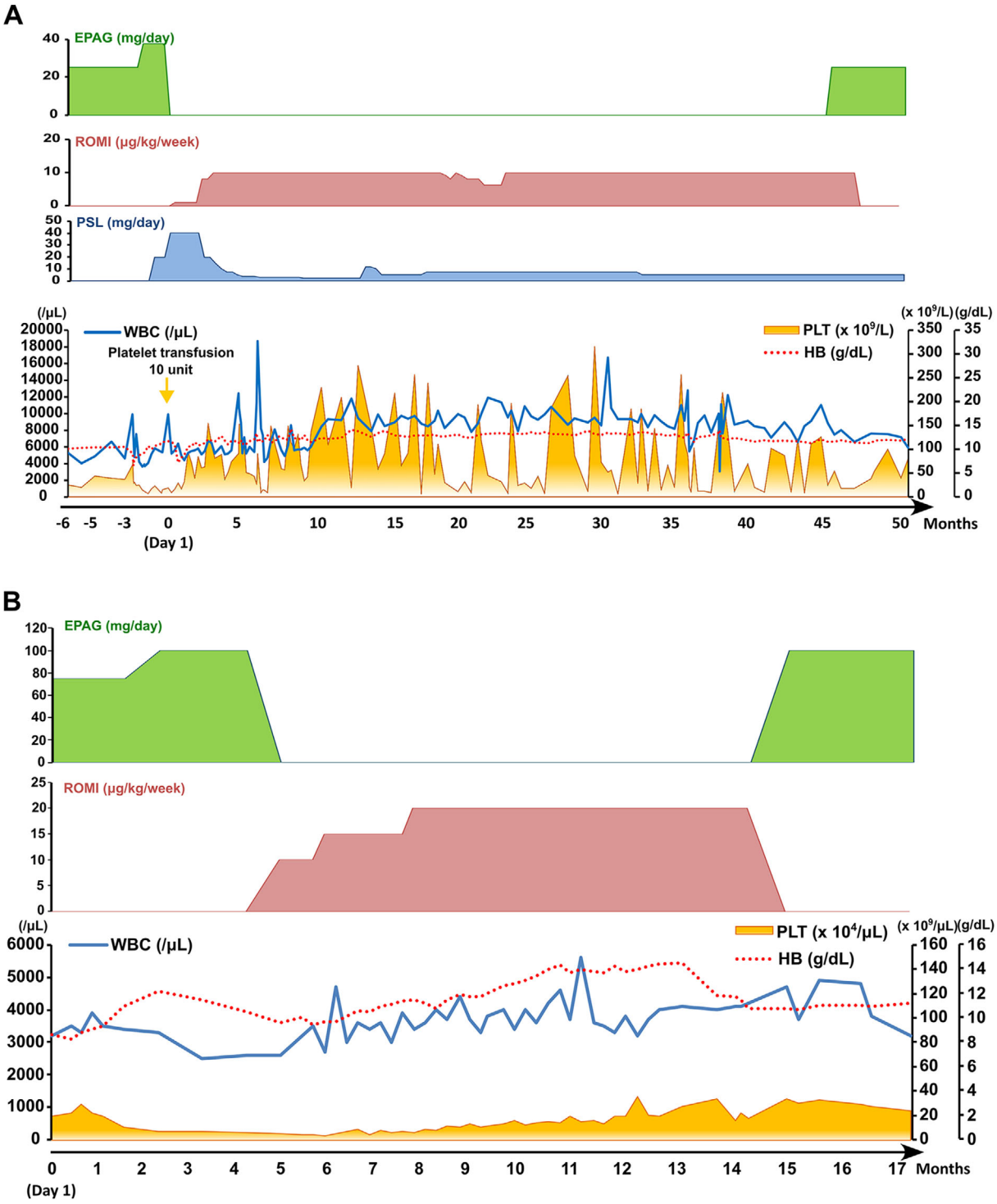


Figure. **Clinical and therapeutic courses, together with alterations in blood cell counts in Case 1 (A) and Case 2 (B). EPAG: eltrombopag, HB: hemoglobin level, PLT: platelet count, PSL: prednisolone, ROMI: romiplostim, WBC: white blood cell count**

adequately understood. Based on previous findings, researchers have proposed that the two TPO-RAs exhibit unequal efficacy and that the cause of TPO-RA non-response may be inadequate dosage (7, 11). Furthermore, as evidence in support of this hypothesis, a case involving a refractory AA patient who exhibited no response to eltrombopag at 75 mg/day but achieved a positive response to 150 mg/day (12). In the two cases discussed here, the initial ineffectiveness of eltrombopag necessitated switching to romiplostim, which produced favorable outcomes.

The reassertion of eltrombopag efficacy in the present case may be explained by several reports of long-term remission after cessation of TPO-RAs in patients with ITP or AA (13-17). One study suggested that this phenomenon may be attributable to increased levels of total circulating transforming growth factor (TGF)-β1, improvements in the quan-

tity and functionality of regulatory T lymphocytes, and the restoration of immune tolerance to platelet autoantibodies (18, 19). Therefore, we hypothesized that eltrombopag, despite its previously ineffective dosage, may have exhibited a response.

In conclusion, we presented two cases of patients with ITP and severe AA who were switched from eltrombopag to romiplostim due to insufficient efficacy and then switched back to eltrombopag. This report provides insights into treatment strategies that are beneficial for ITP and AA patients, who may be challenging to manage in clinical practice.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We express our appreciation for the academic advice and critical evaluations provided by Masamichi Ikawa (University of Fukui).

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets obtained and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Ethical approval

This work was performed in accordance with the Declaration of Helsinki and its amendments and the Ethical Guidelines for Clinical Research from the Ministry of Health, Labour and Welfare, Japan. Written informed consent was obtained from the patients for the publication of their case details.

Author contributions

Kazuhiro Itoh, Nozomi Otsuki, Hiroshi Tsutani, and Hiromichi Iwasaki drafted the article. All of the authors critically revised the manuscript for important intellectual content. All of the authors contributed to the literature search and approval of the final manuscript.

References

1. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv **3**: 3829-3866, 2019.

2. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia. N Engl J Med **386**: 11-23, 2022.

3. Jang JH, Tomiyama Y, Miyazaki K, et al. Efficacy and safety of romiplostim in refractory aplastic anaemia: a Phase II/III, multicentre, open-label study. Br J Haematol **192**: 190-199, 2021.

4. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood **123**: 1818-1825, 2014.

5. Erickson-Miller CL, Delorme E, Tian S-S, et al. Preclinical activity of eltrombopag (SB-497115), an oral, nonpeptide thrombopoietin receptor agonist. Stem Cells **27**: 424-430, 2009.

6. Cwirla SE, Balasubramanian P, Duffin DJ, et al. Peptide agonist of the thrombopoietin receptor as potent as the natural cytokine. Science **276**: 1696-1699, 1997.

7. Khellaf M, Viallard J-F, Hamidou M, et al. A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. Haematologica **98**: 881-887, 2013.

8. Hosokawa K, Yamazaki H, Tanabe M, Imi T, Sugimori N, Nakao S. High-dose romiplostim accelerates hematologic recovery in patients with aplastic anemia refractory to eltrombopag. Leukemia **35**: 906-909, 2021.

9. Sugimori C, Chuhjo T, Feng X, et al. Minor population of CD55-CD59- blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood **107**: 1308-1314, 2006.

10. Bussel J, Kulasekararaj A, Cooper N, et al. Mechanisms and therapeutic prospects of thrombopoietin receptor agonists. Semin Hematol **56**: 262-278, 2019.

11. Lakhwani S, Perera M, Fernández-Fuertes F, et al. Thrombopoietin receptor agonist switch in adult primary immune thrombocytopenia patients: A retrospective collaborative survey involving 4 Spanish centres. Eur J Haematol **99**: 372-377, 2017.

12. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia. N Engl J Med **367**: 11-19, 2012.

13. Ghadaki B, Nazi I, Kelton JG, Arnold DM. Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists. Transfusion **53**: 2807-2812, 2013.

14. Mahévas M, Fain O, Ebbo M, et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. Br J Haematol **165**: 865-869, 2014.

15. Červinek L, Mayer J, Doubek M. Sustained remission of chronic immune thrombocytopenia after discontinuation of treatment with thrombopoietin-receptor agonists in adults. Int J Hematol **102**: 7-11, 2015.

16. González-López TJ, Pascual C, Álvarez-Román MT, et al. Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. Am J Hematol **90**: E40-E43, 2015.

17. Desmond R, Townsley DM, Dunbar C, Young NS. Eltrombopag in aplastic anemia. Semin Hematol **52**: 31-37, 2015.

18. Bao W, Bussel JB, Heck S, et al. Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. Blood **116**: 4639-4645, 2010.

19. Nishimoto T, Numajiri M, Nakazaki H, Okazaki Y, Kuwana M. Induction of immune tolerance to platelet antigen by short-term thrombopoietin treatment in a mouse model of immune thrombocytopenia. Int J Hematol **100**: 341-344, 2014.

frontiers | Frontiers in Pharmacology

TYPE Opinion
PUBLISHED 09 October 2025
DOI 10.3389/fphar.2025.1691613

OPEN ACCESS

EDITED BY
Qinghe Meng,
Upstate Medical University, United States

REVIEWED BY
Mustafa Can Guler,
Atatürk University, Türkiye

*CORRESPONDENCE
Kazuhiro Itoh,
kitoh@u-fukui.ac.jp

RECEIVED 24 August 2025
ACCEPTED 02 October 2025
PUBLISHED 09 October 2025

CITATION
Itoh K, Tsutani H, Mitsuke Y, Ikawa M and Iwasaki H (2025) Potential strategies for combination therapy involving medicines with differential signal transduction regulation effects and the mechanism of action of minocycline in septic neuroinflammation. *Front. Pharmacol.* 16:1691613. doi: 10.3389/fphar.2025.1691613

Potential strategies for combination therapy involving medicines with differential signal transduction regulation effects and the mechanism of action of minocycline in septic neuroinflammation

Kazuhiro Itoh [1,2]*, Hiroshi Tsutani[1], Yasuhiko Mitsuke[1], Masamichi Ikawa[2] and Hiromichi Iwasaki[2]

[1]Department of Internal Medicine, NHO Awara National Hospital, Awara, Japan, [2]Department of Community Health Science, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

KEYWORDS

brain inflammation, sepsis, minocycline, toll-like receptor 4, combination therapy

Introduction

Sepsis-associated encephalopathy (SAE) shows diffuse dysfunctions. Hosseini et al. recently suggested that minocycline could be an effective medication for avoiding neurological complications associated with sepsis. They demonstrated that in a murine model of lipopolysaccharide (LPS) treatment, minocycline attenuated the brain inflammation and oxidative stress induced by sepsis in a dose-dependent manner (Hosseini et al., 2024). We have previously established that minocycline modulates the production of inflammatory cytokines and chemokines by inhibiting inhibitor of nuclear factor κB (IκB) kinase (IKK)α/β, a downstream signaling molecule of Toll-like receptor 4 (TLR4), in LPS-stimulated THP-1 cells (Tai et al., 2013). Based on these results, we suggest that minocycline helps the body by affecting sepsis-related brain inflammation, which is mainly controlled by microglia through TLR4-dependent pathways. This study evaluates the significance of combination therapy for SAE in two key aspects: first, the combination of minocycline with fluoroquinolones. The distinct mechanisms of action—where fluoroquinolones obstruct the upstream signaling pathway of sepsis (TLR4/MD-2 complex formation) and minocycline inhibits the downstream pathway (IKKα/β phosphorylation)—support the hypothesis that targeting various points within the same pathway amplifies the modulatory effect on neuroinflammation. Secondly, combination therapy utilizes minocycline alongside additional signal transduction pathway inhibitors. The pathophysiology of SAE encompasses the TLR4/NF-κB pathway as well as various signal transduction pathways, including mitogen-activated protein kinase (MAPK), Janus kinase/signal transduction and activator of transcription (JAK/STAT), and Nod-like receptor protein 3 (NLRP3) inflammasome, among others. Therefore, we investigated the potential of a multifaceted therapeutic strategy that integrates inhibitors aimed at each of these signaling pathways. The combination strategies outlined in this research are grounded in a theoretical framework established from

TABLE 1 Key studies on the role of minocycline and fluoroquinolones in neuroinflammation.

Authors (year)	Study type	Experimental model	Key findings	Relevance to this study
Minocycline				
Hosseini et al. (2024)	*In vivo*	Mouse LPS sepsis model	Minocycline decreased brain inflammation and oxidative stress in a dose-dependent fashion and facilitated recovery in mice	This offers concrete data supporting the hypothesis of this study, specifically that minocycline inhibits septic neuroinflammation
Tai et al. (2013)	*In vitro*	Human monocyte-like cell line (THP-1 cells)	Minocycline inhibited the synthesis of inflammatory cytokines triggered by LPS stimulation. This effect was facilitated by the suppression of IKKα/β phosphorylation downstream of TLR4	This provides direct evidence for the mechanism suggested in this study, specifically that minocycline inhibits downstream signaling of the TLR4/NF-κB pathway
Zou et al. (2025)	*In vivo/ in vitro*	Mouse *Staphylococcus aureus* infection model/microglia cells	Minocycline demonstrated neuroprotective benefits through the modulation of the TLR2 and STAT3 pathways	This article is crucial for illustrating the variety of mechanisms of action and broadening the discussion to pathways beyond TLR4
Yrjänheikki et al. (1998)	*In vivo*	Rat cerebral ischemia model	Minocycline inhibited microglial activation and caspase-1 expression following cerebral ischemia, exhibiting neuroprotective effects	A notable piece of evidence indicates that minocycline has been recognized for its role as an inhibitor of microglial activation for an extended period
Fluoroquinolone				
Zusso et al. (2019)	*In vitro*	Primary cultured microglia	Ciprofloxacin and related drugs interact with the TLR4 co-receptor MD-2, blocking the assembly of the LPS-TLR4 complex and thereby reducing NF-κB activation and cytokine synthesis	This presents significant evidence supporting the combination therapy concept that fluoroquinolones impede the upstream TLR4/NF-κB pathway

current literature. This paper proposes a novel therapeutic idea, the efficacy and safety of which necessitate thorough validation through future preclinical and clinical trials.

Pathophysiology of cytokine storms: from PAMP/DAMP recognition to inflammatory cell death

In sepsis, manifestation of a cytokine storm represents a critical and life-threatening situation. Factors that can trigger a cytokine storm include the interaction between pathogen-associated molecular patterns (PAMPs), like LPS from pathogens, and damaged cell-associated molecular patterns (DAMPs), which are produced after cells die or get hurt, along with pattern recognition receptors (PRRs). This interaction results in the overproduction of inflammatory cytokines in mammals. Cytokines are closely linked to mammalian cell death mechanisms, where cytokine signaling or PAMP/DAMP recognition can initiate inflammatory cell death. This process enhances the release of pathogenic cytokines via a positive feedback loop, ultimately resulting in the cytokine storm and causing serious damage to host tissues and organs, potentially leading to death (Karki and Kanneganti, 2021). In a mouse model of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hemophagocytic lymphohistiocytosis, and sepsis, blocking tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) prevents cell death and reduces the development of cytokine storm (Karki and Kanneganti, 2021). These data suggest that inhibiting the overproduction of inflammatory cytokines is crucial to improving the prognosis of sepsis.

Mechanism of action of minocycline and fluoroquinolones through the inhibition of the TLR4/NF-κB pathway

Monocytes, macrophages, and microglia express PRRs such as TLR4, which identify PAMPs and DAMPs during sepsis, subsequently generating inflammatory cytokines and chemokines via intracellular signaling pathways. In SAE, microglia serve a crucial role in neuroinflammation. The role of TLR4 in neuroinflammation is context-dependent and not uniform. A study has indicated that TLR4 activation may confer neuroprotective effects under specific circumstances (Radpour et al., 2022). In Gram-negative bacterial sepsis, increased TLR4 activation induced by LPS, a principal component of Gram-negative bacteria, is regarded as a key contributor driving the detrimental neuroinflammatory cascade seen in SAE.

In an LPS sepsis model utilizing THP-1 cells as a monocyte surrogate, we demonstrated that minocycline dose-dependently inhibited the production of inflammatory cytokines such as TNF-α, interleukin (IL)-6, and IFN-γ, as well as chemokines including IL-8 and interferon-inducible protein (IP)-10 (Tai et al., 2013). The immunomodulatory effects of minocycline extend beyond the previously reported LPS-stimulated THP-1 cell model and the LPS sepsis mouse model described by Hosseini et al. The neuroprotective effects and anti-inflammatory properties have been investigated for decades across many disease models. Likewise, the immunomodulatory effects of fluoroquinolones have been reported. To elucidate the context of the discussion in this study, we summarize the pertinent research findings below (Table 1). According to Table 1, the neuroprotective effects of minocycline are multifaceted, indicating that its mechanism of action is not restricted to the inhibition of the TLR4 pathway by LPS stimulation but also involves the TLR2 pathway in response to

stimulation by various pathogens (*Staphylococcus aureus*) (Zou et al., 2025). Moreover, it has been established that the activation of microglia can be inhibited in non-infectious conditions, such as cerebral ischemia (Yrjänheikki et al., 1998). The consistent findings indicating that minocycline mitigates neuroinflammation across multiple models support its potential as a treatment candidate for SAE. This study concentrates on the TLR4 pathway, crucial in Gram-negative bacterial sepsis associated with LPS. Fluoroquinolones represent a theoretically advantageous upstream inhibitor for minocycline. We suggest an innovative treatment theory utilizing fluoroquinolones that inhibit upstream TLR4 signaling by binding to the TLR4 co-receptor, MD-2, thereby preventing the formation of the LPS-TLR4 complex (Zusso et al., 2019). This unique approach, focusing on the first phase of the signaling cascade, complements minocycline's effect on the downstream pathway (IKKα/β phosphorylation) (Tai et al., 2013). This dual-target strategy constitutes the fundamental justification for our proposed combination.

Antibacterial efficacy of the combination use of tetracycline and fluoroquinolone

Minocycline and fluoroquinolones exhibit considerable overlap in their antimicrobial spectra, and our literature review failed to find any definitive evidence concerning their synergistic antimicrobial activity; however, we found several studies of efficacy in specific situations (Supplementary Table S1). It is important to acknowledge that these clinical instances do not directly pertain to SAE. Although they present intriguing instances illustrating the possible advantages of combining tetracycline and fluoroquinolone drugs, their pathophysiology circumstances markedly diverge from SAE. Therefore, caution must be observed when generalizing these findings to the management of SAE.

Stenotrophomonas maltophilia exhibits significant susceptibility to trimethoprim-sulfamethoxazole (TMP/SMX), the primary therapy. The IDSA guidelines recommend the combination of the following medications for *S. maltophilia*: TMP/SMX, minocycline, levofloxacin, cefiderocol, or the combination of ceftazidime/avibactam and aztreonam (Tamma et al., 2024).

In the context of brucellosis treatment, patients receiving the doxycycline-rifampin combination therapy had a significantly higher recurrence rate than those receiving doxycycline-rifampin-levofloxacin combination therapy (22.6% vs. 9.3%, p-value = 0.01). The incidence rate of treatment-related side effects did not exhibit a statistically significant difference (20.4% vs. 11.3%, p-value = 0.059) (Hasanain et al., 2016).

In comparison to levofloxacin monotherapy, the combination of minocycline and levofloxacin markedly postponed the development of levofloxacin-resistant strains in clinical isolates of *Elizabethkingia anophelis* and inhibited the establishment of DNA gyrase mutations even after numerous passages (Lee et al., 2024).

A randomized controlled trial of *Helicobacter pylori* eradication therapy demonstrated that a four-drug regimen incorporating tetracycline and levofloxacin as a salvage therapy for primary treatment failure significantly enhanced eradication rates compared to the standard four-drug regimen of clarithromycin and amoxicillin (82.1% vs. 70.1%, P = 0.0001) (Alavinejad et al., 2023).

Japanese spotted fever (JSF), a rickettsial illness, exemplifies sepsis by inducing an excessive release of inflammatory cytokines and chemokines during disease onset (Tai et al., 2014). In a recent meta-analysis of body temperature data from JSF case reports, we identified a significant hypothermic effect in the tetracycline and fluoroquinolone combination group in comparison to the tetracycline monotherapy group. This serves as a specific example of clinical cases receiving the combination of tetracycline and fluoroquinolones (Itoh et al., 2023).

Although there is no established evidence that the combination of tetracycline and fluoroquinolones augments antibacterial efficacy concerning SAE, it is intriguing to observe that the benefits of combining these two antibiotics have been demonstrated in several clinical cases.

A framework for combination therapy targeting interconnected signaling networks in SAE

The TLR4/NF-κB pathway is a vital starter in the pathogenesis of SAE, operating within a complex, interrelated signaling network. To enhance treatment efficacy, it is essential to acknowledge the broader network that includes the major MAPK, JAK/STAT, and NLRP3 inflammasome pathways (Chen et al., 2020; Ren et al., 2020). Figure 1 depicts the principal signaling pathways related to SAE.

These pathways establish a harmful feedback loop. Activation of TLR4 can initiate the MAPK pathway, which enhances cytokine production. These cytokines subsequently stimulate the JAK/STAT pathway, functioning as a potent "amplification loop" for the inflammatory response. Concurrently, danger signals arising from cellular damage can trigger the NLRP3 inflammasome, resulting in the generation of powerful cytokines such as IL-1β and IL-18. The suppression of each of these pathways has exhibited neuroprotective effects in preclinical SAE models (Liu et al., 2022; Bhadauriya et al., 2025; Chen et al., 2020; Zhong et al., 2020).

Given the significant interplay among various systems, a multifaceted therapeutic strategy is a more logical approach than focusing on a singular channel. We offer a strategy for combination therapy that concurrently targets both the "initiation signals" and the "amplification signals" of neuroinflammation. For instance, the combination of minocycline (a modulator of the TLR4 pathway) with a JAK inhibitor could simultaneously reduce the initial inflammatory stimulus and the next cytokine-mediated amplification loop. This method may provide substantial neuroprotective effects that monotherapy cannot provide. This idea necessitates validation in forthcoming trials to ascertain the efficacy and safety of these combination treatments in pertinent SAE models.

Adverse events (particularly in antibiotics)

A cohort study revealed that the median age (IQR) of 2,780 SAE patients was 67 (56–76.8) (Lu et al., 2023). Another study into

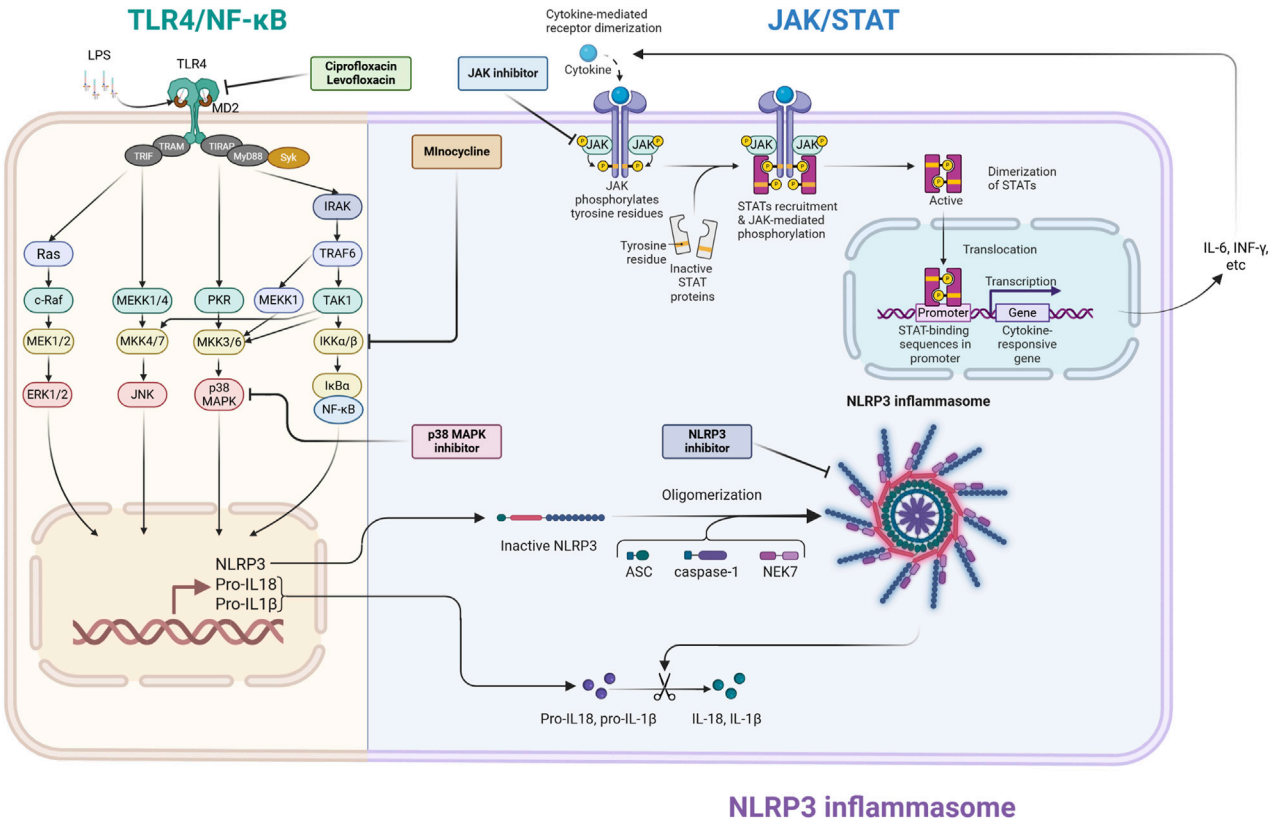


FIGURE 1
Schematic illustration of principal neuroinflammatory signaling pathways and treatment targets in septic encephalopathy (SAE). This illustration depicts the interactions among the three principal inflammatory signaling pathways (TLR4/NF-κB, NLRP3 inflammasome, and JAK/STAT) implicated in the pathogenesis of SAE, along with the pharmacological targets for these pathways. TLR4/NF-κB signaling pathway: Bacterial-derived lipopolysaccharides (LPS) interact with the TLR4/MD2 complex, initiating intracellular signaling pathways that result in the nuclear translocation of the transcription factor NF-κB. This facilitates the transcription of inflammatory cytokines and the precursors of NLRP3 inflammasome substrates, pro-IL-1β and pro-IL-18 (priming signal). Fluoroquinolone drugs (ciprofloxacin, levofloxacin) obstruct the interaction of LPS with TLR4 at the proximal segment of this route. This pathway also stimulates the MAPK pathway, which is inhibited by p38 MAPK inhibitors. NLRP3 inflammasome: NLRP3 assembles an inflammasome complex with ASC and caspase-1 in response to diverse intracellular stressors. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18, resulting in the production and release of the potent inflammatory cytokines IL-1β and IL-18 (activation signal). NLRP3 inhibitors impede the assembly of this complex. JAK/STAT signaling pathway: Inflammatory cytokines (IL-6, IFN-γ, etc.) generated by NF-κB attach to cell surface receptors, activating JAKs linked to these receptors, which subsequently phosphorylate STATs. Activated STATs dimerize and translocate to the nucleus, facilitating the synthesis of supplementary inflammatory cytokines. This operates as a positive feedback loop that significantly enhances the inflammatory response. JAK inhibitors are proposed to obstruct JAK activation, whereas minocycline may impede receptor activation by cytokines. This illustration visually represents the theoretical foundation for "multimodal combination therapy," which integrates pharmacological agents with distinct modes of action to tackle the intricate pathophysiology of SAE. ASC, apoptosis-associated speck-like protein containing caspase recruitment domain; ERK, extracellular signal-regulated kinase; IFN-γ, interferon-gamma; IκBα, inhibitor of nuclear factor kappa-B kinase alpha; IKKα/β, IκB kinase alpha/beta; IL-6, interleukin-6; IRAK, IL-1 receptor-related kinase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEKK, mitogen-activated protein/ERK kinase kinase; MD2, myeloid differentiation factor 2; MKK, mitogen-activated protein kinase kinase; MyD88, myeloid differentiation factor 88; NEK7, NIMA-related protein kinase 7; NF-κB, nuclear factor kappa-B; NLRP3, Nod-like receptor protein 3; PKR, double-stranded RNA-activated protein kinase; STAT, signal transduction and activator of transcription; Syk, spleen tyrosine kinase; TAK1, transforming growth factor-β-activated kinase 1; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain-containing adaptor protein; TLR, toll-like receptor; TRAF, tumor necrosis factor receptor associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor protein inducing interferon-β. The figure was created using BioRender (https://biorender.com/).

pediatric SAE revealed that children exhibit heightened vulnerability to metabolic irregularities typically observed in PICUs, thereby elevating their risk of developing SAE relative to adults. The limited incidence of reported cases and fatalities from pediatric SAE is largely attributable to underreporting or underdiagnosis, underscoring this as a significant clinical concern (Dumbuya et al., 2023). Furthermore, numerous studies have expressed apprehensions over adverse events linked to the use of antibiotics in pediatric SAE patients (Chen et al., 2022; de Araújo et al., 2022; Gong et al., 2022; Dumbuya et al., 2023).

Minocycline may result in tooth discoloration, enamel hypoplasia, and temporary bone growth abnormalities in children, particularly those under 8 years of age during dental development, as indicated in the manufacturer's package insert. Moreover, fluoroquinolones may impact joints and cartilage throughout pediatric development, and their administration in children is strictly prohibited save for specific exceptions (e.g., tosufloxacin). Furthermore, concerns regarding adverse events in geriatric patients, including tendinopathy and central nervous system effects, are extensively reported and restrict their

application in another significant SAE demographic. The substantial safety issues, especially in at-risk pediatric and geriatric groups, provide a considerable obstacle to the clinical implementation of this suggested combination therapy and must be carefully evaluated against any potential advantages. As a result, meticulous selection and use of antibiotics are crucial for pediatric patients.

Secondly, the risk of antibiotic resistance arising from microbiome perturbations is a universal concern for all antimicrobial drugs, and the significance of cautious antimicrobial usage is widely acknowledged. Specifically, concurrent use of two or more antibacterial agents increases the likelihood of adverse effects. This encompasses significant disruptions of the gut microbiota, potentially resulting in problems such as *Clostridioides difficile* infection, and may have enduring effects on host immunity. Moreover, the synergistic pressure of two antibiotics might expedite the emergence and selection of multidrug-resistant organisms, a significant public health issue. Therefore, the unnecessary application of such combination antimicrobial therapy must be stringently avoided and should only be contemplated when a definitive, significant advantage is expected.

Limitations

This document aims to suggest a novel treatment hypothesis grounded in existing knowledge, rather than to present new experimental results. Minocycline and fluoroquinolones may have synergistic effects in protecting against sepsis-associated neuroinflammation through distinct mechanisms. However, there is presently no direct experimental evidence, so this suggestion remains a working hypothesis at present. This remains a hypothesis that necessitates further validation via such studies as animal experiments using the SAE model mice and clinical trials involving humans. Tetracycline and fluoroquinolones target distinct components of the TLR4 pathway; nonetheless, SAE entails intricate interactions with additional signaling pathways. Thus, it is essential to evaluate solutions that address not only the impacts on the TLR4 pathway but also more extensive modes of action. The pathophysiological mechanisms of JSF and other bacterial situations, and SAE are distinct, thereby restricting the relevance of the data to SAE.

Conclusion

We suggest a mechanism via which minocycline exerts an inhibitory effect on neuroinflammation in SAE. This study primarily identified the inhibitory mechanism as depending on the TLR4 signaling pathway. Ultimately, this paper presents a hypothesis-generating proposal that is intended to promote additional research. Future research is expected to examine therapeutic possibilities that involve the manipulation of various signaling pathways associated with SAE and to substantiate the notions outlined above.

Author contributions

KI: Data curation, Writing – review and editing, Methodology, Writing – original draft, Formal Analysis, Investigation, Visualization, Resources, Conceptualization, Validation, Project administration. HT: Methodology, Supervision, Writing – review and editing, Writing – original draft, Conceptualization, Investigation, Project administration, Validation. YM: Conceptualization, Project administration, Writing – review and editing, Methodology, Supervision, Validation, Investigation, Writing – original draft. MI: Project administration, Validation, Methodology, Supervision, Writing – review and editing, Writing – original draft, Investigation, Conceptualization. HI: Validation, Methodology, Investigation, Supervision, Writing – review and editing, Conceptualization, Project administration, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1691613/full#supplementary-material

References

Alavinejad, P., Nayebi, M., Parsi, A., Abdelsameea, E., Ahmed, M. H., Hormati, A., et al. (2023). Levofloxacin+Tetracycline quadruple regimen for eradication of *helicobacter Pylori*: a multicenter multinational randomized controlled trial. *Middle East J. Dig. Dis.* 15, 12–18. doi:10.34172/mejdd.2023.314

Bhadauriya, M. S., Singh, H., Suri, M., Hanifa, M., and Bali, A. (2025). JAK/STAT inhibitors mitigate sepsis-associated cerebral and cognitive injury. *Fundam. Clin. Pharmacol.* 39, e70005. doi:10.1111/fcp.70005

Chen, S., Tang, C., Ding, H., Wang, Z., Liu, X., Chai, Y., et al. (2020). Maf1 ameliorates sepsis-associated encephalopathy by suppressing the NF-kB/NLRP3 inflammasome signaling pathway. *Front. Immunol.* 11, 594071. doi:10.3389/fimmu.2020.594071

Chen, Y., Hu, Y., Li, X., Chen, P., Wang, C., Wang, J., et al. (2022). Clinical features and factors associated with sepsis-associated encephalopathy in children: retrospective single-center clinical study. *Front. Neurol.* 13, 838746. doi:10.3389/fneur.2022.838746

de Araújo, B. E. S., da Silva Fontana, R., de Magalhães-Barbosa, M. C., Lima-Setta, F., Paravidino, V. B., Riveiro, P. M., et al. (2022). Clinical features, electroencephalogram, and biomarkers in pediatric sepsis-associated encephalopathy. *Sci. Rep.* 12, 10673. doi:10.1038/s41598-022-14853-z

Dumbuya, J. S., Li, S., Liang, L., and Zeng, Q. (2023). Paediatric sepsis-associated encephalopathy (SAE): a comprehensive review. *Mol. Med.* 29, 27. doi:10.1186/s10020-023-00621-w

Gong, X., Weng, B., Zhang, X., Yan, C., and Cai, C. (2022). The molecular basis of brain injury in preterm infants with sepsis - associated encephalopathy. *BMC Pediatr.* 22, 336. doi:10.1186/s12887-022-03372-5

Hasanain, A., Mahdy, R., Mohamed, A., and Ali, M. (2016). A randomized, comparative study of dual therapy (doxycycline-rifampin) versus triple therapy (doxycycline-rifampin-levofloxacin) for treating acute/subacute brucellosis. *Braz J. Infect. Dis.* 20, 250–254. doi:10.1016/j.bjid.2016.02.004

Hosseini, M., Bardaghi, Z., Askarpour, H., Rajabian, A., Mahmoudabady, M., Shabab, S., et al. (2024). Minocycline mitigates sepsis-induced neuroinflammation and promotes recovery in male mice: insights into neuroprotection and inflammatory modulation. *Physiol. Rep.* 12, e70032. doi:10.14814/phy2.70032

Itoh, K., Kabata, D., Shigemi, H., Hirota, T., Sakamaki, I., Tsutani, H., et al. (2023). Evaluation of tetracycline and fluoroquinolone therapy against Japanese spotted fever: analysis based on individual data from case reports and case series. *Int. J. Antimicrob. Agents* 62, 106895. doi:10.1016/j.ijantimicag.2023.106895

Karki, R., and Kanneganti, T.-D. (2021). The "cytokine storm": molecular mechanisms and therapeutic prospects. *Trends Immunol.* 42, 681–705. doi:10.1016/j.it.2021.06.001

Lee, C.-C., Lai, C.-H., Yang, C.-H., Huang, Y.-H., and Lin, J.-N. (2024). Antibiotic combination to effectively postpone or inhibit the *in vitro* induction and selection of levofloxacin-resistant mutants in *Elizabethkingia anophelis*. *Int. J. Mol. Sci.* 25, 2215. doi:10.3390/ijms25042215

Liu, Y.-X., Yu, Y., Liu, J.-P., Liu, W.-J., Cao, Y., Yan, R.-M., et al. (2022). Neuroimmune regulation in sepsis-associated encephalopathy: the interaction between the brain and peripheral immunity. *Front. Neurol.* 13, 892480. doi:10.3389/fneur.2022.892480

Lu, X., Qin, M., Walline, J. H., Gao, Y., Yu, S., Ge, Z., et al. (2023). Clinical phenotypes of sepsis-associated encephalopathy: a retrospective cohort study. *Shock* 59, 583–590. doi:10.1097/SHK.0000000000002092

Radpour, M., Choopani, S., Pourbadie, H. G., and Sayyah, M. (2022). Activating toll-like receptor 4 after traumatic brain injury inhibits neuroinflammation and the accelerated development of seizures in rats. *Exp. Neurol.* 357, 114202. doi:10.1016/j.expneurol.2022.114202

Ren, C., Yao, R.-Q., Zhang, H., Feng, Y.-W., and Yao, Y.-M. (2020). Sepsis-associated encephalopathy: a vicious cycle of immunosuppression. *J. Neuroinflammation* 17, 14. doi:10.1186/s12974-020-1701-3

Tai, K., Iwasaki, H., Ikegaya, S., and Ueda, T. (2013). Minocycline modulates cytokine and chemokine production in lipopolysaccharide-stimulated THP-1 monocytic cells by inhibiting IκB kinase α/β phosphorylation. *Transl. Res.* 161, 99–109. doi:10.1016/j.trsl.2012.10.001

Tai, K., Iwasaki, H., Ikegaya, S., Takada, N., Tamaki, Y., Tabara, K., et al. (2014). Significantly higher cytokine and chemokine levels in patients with Japanese spotted fever than in those with tsutsugamushi disease. *J. Clin. Microbiol.* 52, 1938–1946. doi:10.1128/JCM.03238-13

Tamma, P. D., Heil, E. L., Justo, J. A., Mathers, A. J., Satlin, M. J., and Bonomo, R. A. (2024). Infectious diseases society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. *Clin. Infect. Dis.*, ciae403. doi:10.1093/cid/ciae403

Yrjänheikki, J., Keinänen, R., Pellikka, M., Hökfelt, T., and Koistinaho, J. (1998). Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. *Proc. Natl. Acad. Sci. U. S. A.* 95, 15769–15774. doi:10.1073/pnas.95.26.15769

Zhong, X., Xie, L., Yang, X., Liang, F., Yang, Y., Tong, J., et al. (2020). Ethyl pyruvate protects against sepsis-associated encephalopathy through inhibiting the NLRP3 inflammasome. *Mol. Med.* 26, 55. doi:10.1186/s10020-020-00181-3

Zou, J., Gao, J., Shang, W., and Fan, X. (2025). Minocycline ameliorates *staphylococcus aureus*-induced neuroinflammation and anxiety-like behaviors by regulating the TLR2 and STAT3 pathways in microglia. *Brain Sci.* 15, 128. doi:10.3390/brainsci15020128

Zusso, M., Lunardi, V., Franceschini, D., Pagetta, A., Lo, R., Stifani, S., et al. (2019). Ciprofloxacin and levofloxacin attenuate microglia inflammatory response via TLR4/NF-kB pathway. *J. Neuroinflammation* 16, 148. doi:10.1186/s12974-019-1538-9

International Journal of Infectious Diseases 155 (2025) 107899

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Medical Imagery

Paecilomyces variotii isolated from the blood of a patient with rheumatoid arthritis-related interstitial pneumonia

Kazuhiro Itoh[1,2,*], Daiki Maruno[3], Nozomi Otsuki[1], Hiroshi Tsutani[1], Yasuhiko Mitsuke[1], Hiromichi Iwasaki[2]

[1] *Department of Internal Medicine, NHO Awara National Hospital, Awara, Fukui, Japan*
[2] *Division of Infection Control and Prevention, University of Fukui Hospital, Fukui, Fukui, Japan*
[3] *Department of Laboratory Medicine, NHO Awara National Hospital, Awara, Fukui, Japan*

ARTICLE INFO

Article history:
Received 22 January 2025
Revised 27 March 2025
Accepted 28 March 2025

Keywords:
Paecilomyces variotii
Filamentous fungus
Blood culture
Rheumatoid arthritis

Medical imagery

A 73-year-old female with rheumatoid arthritis-related interstitial pneumonia was hospitalized due to fever and suspected bacterial pneumonia (Day 1). On Day 5, blood cultures showed fungal growth. The colonies were flat, with a powdery or velvety texture and a yellowish-brown to sandy color (Figure 1A). Microscopic

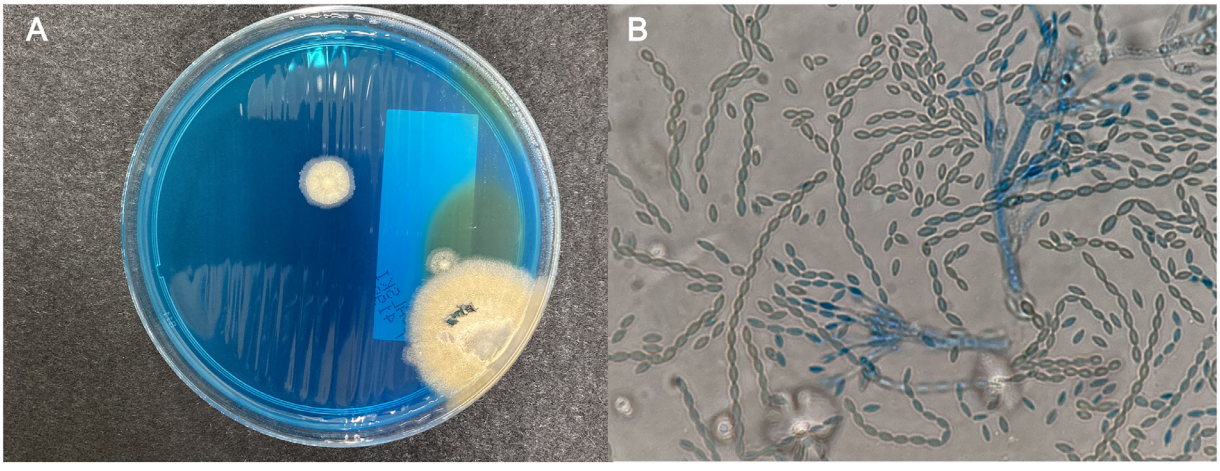


Figure 1. (a) Fungal colonies cultivated on bromothymol blue agar that were derived from blood cultures. (b) Microscopic image of *Paecilomyces variotii* stained with lactophenol cotton blue taken at a higher magnification (200×).

* Corresponding author: Kazuhiro Itoh, Department of Internal Medicine, NHO Awara National Hospital, 238-1 Kitagata, Awara, Fukui 910-4272, Japan.
E-mail address: kitoh@u-fukui.ac.jp (K. Itoh).

https://doi.org/10.1016/j.ijid.2025.107899

analysis demonstrated that the conidia had a dense, vertically oriented configuration of phialides, which were cylindrical or oval, tapering sharply to a lengthy cylindrical neck (Figure 1B). Furthermore, mass spectrometry (BD Bruker MALDI Biotyper Sirius system [Becton, Dickinson, and Company]) identified the isolated fungus as *Paecilomyces variotii* (score value: 2.00).

The spores of *P. variotii* are irregularly branched with brush-like conidia and apical phialides. The phialides have a swollen base that gradually narrows to a pointed apex [1]. *Paecilomyces* mainly comprises *P. variotii* and Paecilomyces *lilacinus*. However, *P. lilacinus* was reclassified as *Purpureocillium lilacinum* in 2011 [2]. *P. variotii* colonies are yellowish-brown [3], whereas *P. lilacinum* colonies are light purple/pink [2], allowing for their differentiation. Fungemia due to *P. variotii* is rare (Table S1); it has been mainly reported in cases with pneumonia or peritonitis in immunocompromised individuals, diabetic patients, or those undergoing continuous peritoneal dialysis [1]. Although our patient received no antifungals, the symptoms ameliorated and there was no recurrence, indicating she was a carrier [4]. We believe she contracted *P. variotii* through the respiratory tract, the main infection route, despite a negative sputum culture [5]. Bloodstream infections due to *P. variotii* can be fatal and require long-term treatment; therefore, if the fungus is isolated from blood, careful consideration of the patient's condition is needed to determine the appropriate treatment plan.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This work was performed in accordance with the tenets of the Declaration of Helsinki and its amendments, and the Ethical Guidelines for Clinical Research from the Ministry of Health, Labour and Welfare, Japan.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Author contributions

Kazuhiro Itoh: Conceptualization, data curation, writing—original draft, writing—review and editing. Daiki Maruno: Conceptualization, data curation, writing—review and editing. Nozomi Otsuki and Yasuhiko Mitsuke: Writing—review and editing. Hiroshi Tsutani: Writing—original draft, writing—review and editing. Hiromichi Iwasaki: Conceptualization, writing—original draft, writing—review and editing, supervision.

Declarations of competing interest

The authors have no competing interests to declare.

Acknowledgments

We express appreciation for the academic advice and critical evaluation provided by Masamichi Ikawa (University of Fukui).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107899.

References

[1] Bellanger AP, Cervoni JP, Faucher JF, Weil-Verhoeven D, Ginet M, Deconinck E, et al. *Paecilomyces variotii* fungemia in a patient with lymphoma needing liver transplant. *Mycopathologia* 2017;**182**:761–5.
[2] Luangsa-Ard J, Houbraken J, van Doorn T, Hong SB, Borman AM, Hywel-Jones NL, et al. *Purpureocillium*, a new genus for the medically important *Paecilomyces lilacinus*. *FEMS Microbiol Lett* 2011;**321**:141–9.
[3] Rimawi RH, Carter Y, Ware T, Christie J, Siraj D. Use of voriconazole for the treatment of *Paecilomyces lilacinus* cutaneous infections: case presentation and review of published literature. *Mycopathologia* 2013;**175**:345–9.
[4] Akhunov VM, Akhunova AM, Lavrent'eva TP. Hypereosinophilic syndrome associated with sepsis due to *Paecilomyces fungi* disseminated into the liver [in Russian]. *Klin Med (Mosk)* 2016;**94**:149–52.
[5] Akhunova AM. Infectious-allergic bronchopulmonary paecilomycosis [in Russian]. *Ter Arkh* 1991;**63**:19–24.

Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6634-25
Intern Med Advance Publication
http://internmed.jp

【 CASE REPORT 】

Anti-citrullinated Protein Antibody-positive Arthralgia Associated with an L110P-E148Q Double Heterozygote: A Case-based Review

Kazuhiro Itoh[1,2], Hiroshi Tsutani[1], Nozomi Otsuki[1], Atsushi Kuwata[1], Chiyo Kiriba[1], Yoshimasa Urasaki[1], Masamichi Ikawa[2], Hiromichi Iwasaki[2] and Yasuhiko Mitsuke[1]

Abstract:
A 42-year-old woman with positive anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) levels exhibited arthralgia, but she did not fulfill the criteria for rheumatoid arthritis (RA). Subsequently, the patient exhibited episodic monoarthritis with a remarkable response to colchicine. An analysis of the *MEFV* gene identified heterozygous variants, L110P and E148Q, thus indicating a colchicine-responsive autoinflammatory condition. The patient was later diagnosed with RA and achieved remission with abatacept and colchicine. This case illustrates that ACPA-positive arthralgia evolves into RA through an autoinflammatory mechanism, thereby underscoring the diagnostic difficulties arising from the convergence of both autoimmune and autoinflammatory characteristics.

Key words: familial Mediterranean fever, anti-cyclic citrullinated peptide antibodies, arthralgia, rheumatoid factor, *MEFV* gene variants

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.6634-25)

Introduction

Autoinflammatory disorders, such as familial Mediterranean fever (FMF), are defined by recurring fever episodes lasting up to three days, accompanied by abdominal pain, chest pain, arthritis, and erysipelas-like erythema, typically observed in the lower extremities. These diseases are distinct from autoimmune disorders, such as rheumatoid arthritis (RA) and infectious diseases (1). FMF is a monogenic autoinflammatory disorder resulting from autosomal recessive variants of the *MEFV* gene, which encodes pyrin, leading to exacerbated inflammation through the activation of the inflammasome and increased production of interleukin (IL)-1 β (1, 2). While FMF may coexist with rheumatic disorders, the occurrence of FMF alongside positive anti-cyclic citrullinated peptide antibodies (ACPA), which are specific to RA, is uncommon (3, 4). Previous research has described several FMF patients with arthritis exhibiting positive results for ACPA, but all individuals tested negative for rheumatoid factor (RF) (5). We present a complex case of a patient diagnosed with ACPA- and RF-positive arthritis who initially did not meet the criteria for RA, but was ultimately diagnosed with RA after experiencing episodes of periodic monoarthritis and showing *MEFV* gene variants.

Case Report

A 42-year-old woman presented to a local rheumatology clinic complaining of pain in the left wrist, both elbows, both knees, and both Achilles tendons (one year before the initial visit to our hospital). Swelling and tenderness were noted over the entire right index finger and around the Achilles tendon; however, no localized swelling in the joint was evident. Laboratory findings at that time were: ACPA 776.1 U/mL (reference range <4.5 U/mL), RF 169 IU/mL (reference range ≤15 IU/mL), C-reactive protein (CRP) < 0.05 mg/dL (reference range ≤0.30 mg/dL), and erythrocyte

[1]Department of Internal Medicine, NHO Awara National Hospital, Japan and [2]Department of Community Health Science, Faculty of Medical Sciences, University of Fukui, Japan
Received: October 1, 2025; Accepted: November 24, 2025; Advance Publication by J-STAGE: February 1, 2026
Correspondence to Dr. Kazuhiro Itoh, kitoh@u-fukui.ac.jp

Table 1. Laboratory Findings.

Peripheral blood		Reference range	Serological tests		Reference range
Red blood cells	5.18×10^{12} /L	3.86–4.92	C-reactive protein	0.01 mg/dL	<0.14
Hemoglobin	14.3 g/dL	11.6–14.8	Erythrocyte sedimentation rate	1 mm/h	3–15
Hematocrit	45.4 %	35.1–44.4	IgG	1,069 mg/dL	820–1,740
White blood cells	4.1×10^{9} /L	3.3–8.6	IgA	108 mg/dL	90–400
Neutrophils	63.6 %	38.3–71.7	IgM	87 mg/dL	52–270
Eosinophils	2.9 %	0.2–7.3	CH50	26 U/mL	30–45
Basophils	0.5 %	0.2–2.0	Anti-nuclear antibodies	<×40	<40
Monocytes	7.8 %	2.7–7.6	ACPA	776.1 U/mL	<4.5
Lymphocytes	25.2 %	21.3–50.2	Rheumatoid factor	112 IU/mL	<15
Platelets	189×10^{9} /L	158–348	Anti-SSA antibodies	<1.0 U/mL	<10.0
Blood chemistry			Anti-SSB antibodies	<1.0 U/mL	<10.0
Total protein	6.1 g/dL	6.5–8.2	Anti-smooth muscle antibodies	<×20	<20
Total bilirubin	0.4 mg/dL	0.4–1.5	Matrix metalloproteinase-3	46.3 mg/mL	17.3–59.7
Aspartate aminotransferase	19 U/L	13–30	**Urinalysis**		
Alanine aminotransferase	10 U/L	7–23	pH	7.0	4.5–7.5
Lactate dehydrogenase	142 U/L	124–222	Protein	Negative	Negative
Alkaline phosphatase	42 U/L	38–113	Glucose	Negative	Negative
Gamma-glutamyl transpeptidase	9 U/L	9–32	Occult blood	Negative	Negative
Creatinine kinase	73 U/L	41–153	White blood cells	<1 /HPF	
Total cholesterol	195 mg/dL	142–248	Red blood cells	<1 /HPF	
Blood urea nitrogen	12.2 mg/dL	8.0–20.0			
Creatinine	0.59 mg/dL	0.46–0.79			

Anti-SSA antibodies: anti-Sjögren's syndrome type A antibodies, Anti-SSB antibodies: anti-Sjögren's syndrome type B antibodies, ACPA: anti-cyclic citrullinated peptide antibodies, CH50: 50% hemolytic complement activity, Ig: immunoglobulin

sedimentation rate (ESR) 2 mm/h. Under a provisional diagnosis of ACPA-positive arthralgia or spondyloarthritis, nonsteroidal anti-inflammatory drugs were administered for two months but proved to be ineffective. The clinic then empirically prescribed 1,000 mg/day of sulfasalazine, which relieved the symptoms; however, the patient requested further examination and was thus referred to our hospital.

At the initial visit (Day 1), the patient complained of pain in both finger joints and Achilles tendons, none of which showed either any apparent swelling or tenderness. Ultrasonography did not reveal any thickening of the synovium, increased blood flow signals in the finger joints, or increased blood flow signals around the Achilles tendon. Table 1 presents test data collected during the first visit to our hospital. No notable new findings were detected except for elevated RF levels and marginally reduced complement levels. At the initial visit, although the patient exhibited elevated levels of ACPA and RF, they did not fulfill the 2010 ACR/EULAR diagnostic criteria for RA, as there was an absence of clinically evident synovitis based on both the physical examination and ultrasound findings. Her human leukocyte antigen types were A2/A24(9) and B7/B62(15). Chest computed tomography revealed no significant findings, including interstitial pneumonia or hilar adenopathy. The patient had no notable family history of autoimmune or inflammatory disorders. The patient was diagnosed with ACPA-positive arthralgia. Treatment with sulfasalazine was continued, and mild pain in the joints and Achilles tendons fluctuated between improvement and exacerbation.

Two years after the initial visit (Day 674), the patient complained of bilateral coxalgia, and ultrasonography revealed synovial thickening and joint effusion in the same areas. We then started methotrexate 8 mg/week in combination with folic acid. Since the start of the new treatment, both the joint and Achilles tendon pain have markedly improved. However, on Day 745, drug-induced liver injury was identified (alanine aminotransferase level, 66 U/L; aspartate aminotransferase level, 138 U/L). The dosage of methotrexate had to be adjusted to a range of 4-6 mg/week.

Around Day 940, the patient developed periodic severe monoarticular pain accompanied by sudden swelling and heat that she had not experienced previously. The pain was not localized, arose in the shoulder, knee, or ankle, and disappeared within 1 or 2 days. Colchicine (1 mg/day) was administered for diagnostic and therapeutic purposes for these newly occurring, periodic episodes of severe monoarticular pain, which had lasted 1-2 days before resolving spontaneously. Colchicine has shown significant efficacy; following its initiation, these acute attacks resolved and no longer recur. This therapeutic response pertained specifically to these acute autoinflammatory flares and did not inhibit the onset of the persistent polyarthritis characteristics of RA. An analysis of *MEFV* identified heterozygous variants at L110P and E148Q. Therefore, we added and maintained colchicine at 1 mg/day as regular oral therapy.

Around Day 1,050, the patient manifested enduring symmetrical polyarthritis of the fingers, wrists, and shoulders. Swelling was confirmed in eight joints (bilateral proximal

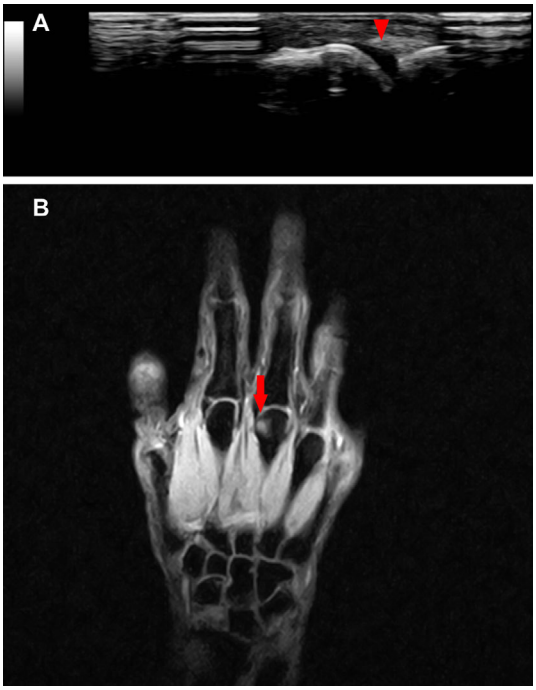


Figure. Imaging findings of the hand on Day 1,102. (A) Ultrasound of the right metacarpophalangeal (MP) joints showing synovial thickening (arrowhead), but no joint effusion or power Doppler signals. (B) T2*-weighted magnetic resonance imaging (MRI) of the right hand, indicating bone erosion at the distal end of the third metacarpal bone (arrow).

interphalangeal, metacarpophalangeal, and metatarsophalangeal joints), and tenderness was noted in 10 joints. Despite the absence of official calculations for disease activity scores, such as the SDAI/CDAI, these findings, along with her elevated levels of ACPA and RF, now fulfilled the 2010 ACR/EULAR categorization criteria for RA for the first time in her clinical course (6). No apparent erosion of the bones was noted on the hand and foot X-rays conducted at the time of RA diagnosis. On Day 1,102, ultrasonography of the right metacarpophalangeal (MP) joints revealed synovial thickening, although without joint effusion or power Doppler signals (Figure A). A subsequent MRI evaluation of the hand confirmed bone erosion at the distal end of the right third metacarpal bone on T2*-weighted images (Figure B). The intravenous infusion of abatacept and a short course of prednisolone were added to colchicine treatment. By Day 1,158, pain in all joints had resolved, joint swelling was no longer present, and the administration of corticosteroids was discontinued.

Search Strategy

We performed a thorough search of PubMed and Ichushi-Web for studies published until May 27, 2025. The search technique employed combinations of the following terms: ("Familial Mediterranean Fever") AND ("anti-cyclic citrullinated peptide antibody" OR "anti-CCP"). Language constraints were not imposed on the dataset. We incorporated case reports, case series, and original articles documenting patients diagnosed with both FMF and ACPA-positive. Conference abstracts, editorials, and review articles that lacked original case data were excluded. Two authors independently evaluated the titles and abstracts, and subsequently retrieved pertinent full-text papers. References of the included articles were manually examined for pertinent supplementary publications. A PRISMA-style flowchart was not created because of the nature of this case-based review; nonetheless, the selection process is detailed in the discussion section.

Discussion

We obtained nine articles via PubMed, three from Ichushi Web, and two through reference searches. Following the elimination of one duplicate document, one conference abstract, one review article, and three unrelated documents, we selected eight articles, comprising five case-control studies and three case reports. The data from the retrieved articles are summarized in Table 2 (4, 5, 7-12).

The case reports detailed three instances of FMF and RA, characterized by elevated RF levels and positive ACPA. These patients fulfilled the diagnostic criteria for RA (4, 9, 12). In our case, despite elevated ACPA and RF levels, no indications of arthritis were noted, thus leading to a diagnosis of ACPA-positive arthralgia in the patient. The symptoms improved slightly with sulfasalazine treatment, but the patient's pain improved significantly with the transition to methotrexate. During treatment, new, previously unobserved, episodic, and severe monoarthritis emerged. Colchicine proved particularly effective for these exacerbations, and a genetic analysis revealed variants of the *MEFV* gene. Subsequently, edema and pain developed in various joints, resulting in a definitive diagnosis of RA (6). Alongside colchicine therapy, treatment with the biological agent abatacept was initiated, leading to the elimination of joint symptoms and remission. This case exemplifies a complicated course of illness marked by the simultaneous presence of autoimmune and autoinflammatory disorders along with gradual advances in both the diagnosis and therapy. We selected abatacept, a T-cell co-stimulation modulator, for the treatment of RA. Owing to the intricate interaction of autoinflammatory and autoimmune characteristics, together with the pivotal function of T-cells in the pathology of RA, abatacept was deemed an appropriate choice. It was selected instead of TNF or IL-6 inhibitors to avoid potential paradoxical effects occasionally documented in autoinflammatory situations; however, evidence for this is limited (13). Recent studies have documented paradoxical inflammatory or autoimmune reactions during TNF-α or IL-6 inhibition, such as psoriasis-like lesions or granulomatous inflammation, even in autoinflammatory disorders such as FMF and Behçet's disease (14, 15). These reactions are thought to stem from dysregulated type I interferon and inflammasome activation, potentially intensifying autoinflammatory predispositions. Furthermore, TNF-α and IL-6 inhibitors have demonstrated inconsistent efficacy in FMF, although IL-1 in-

Table 2. **Literature Review of Familial Mediterranean Fever Patients with Anti-cyclic Citrullinated Peptides Antibodies.**

Authors	Year	Country	Number of patients (n)	Age (years)	Sex (M/F)	WBC ($\times 10^3/mm^3$)	ESR (mm/h)	CRP (mg/dL)	RF levels (IU/mL)	ACPA levels (U/mL)	ACPA positivity rate (%)	Arthritis (%)	Other concomitant manifestations	Gene mutation
Ceri et al.	2010	Turkey	83	30.6±10.7	30/53	7.9±2.4	18.1±16.4	NA	2.1±12.7	14.8±21.1	14.4 (>20 U/mL)	44.6	Abdominal pain: 81.9% Pleuritis: 19.3%	Positivity rate: 92.8% (homozygous 31.1%, heterozygous 68.9%)
Karatay et al.	2010	Turkey	49	26.9±6.2	24/25	NA	11.9±7.1	0.6±0.3	10.0±1.3	NA	0 (>25 U/mL)	46.9	NA	NA
Turan et al.	2010	Turkey	1	48	F	NA	71.0	3.0	412.0	NA	100 (Cut off value: NA)	100	Fever, abdominal pain	M694V homozygous
Uyanik et al.	2010	Turkey	55	33.6±13.5	22/33	7.7±2.1	15.5±15.1	0.6±0.5	8.9±0.8	10.4±14.0	14.5 (>20 U/mL)	36.4	NA	NA
Guler et al.	2012	Turkey	50	31.5 (range: 18-62)	12/38	NA	11 (range: 2-50)	0.4 (range: 0.1-6.4)	NA (positivity rate: 4%, >20 IU/mL)	NA	0 (>12 U/mL)	56.0	Fever: 88% Abdominal pain: 98% Chest pain: 56% Arthralgia: 86% Amyloidosis: 6%	NA
Onur et al.	2013	Turkey	126	11.0±4.0	60/66	NA	20.0±15.0	3.0±12.8	NA	0.97 (IQR: 0.70-1.39)	0 (>20 U/mL)	41.3	Fever: 78.6% Abdominal pain: 73.8% Arthralgia: 41.3%	Positivity rate: 87.3% (M694V homozygous 23.6%, M694V heterozygous 34.5%, other 41.9%)
Migita et al.	2014	Japan	1	51	F	9.2	54.0	0.5	120.0	1,720.0	100 (>4.5 U/mL)	100	Fever	Heterozygous mutations (E148Q/G304R/P369S/R408Q)
Yago et al.	2020	Japan	1	42	F	NA	NA	0.4	64.0	11.2	100 (Cut off value: NA)	100	No fever	R304R homozygous
This case		Japan	1	42	F	4.1	1.0	<0.1	112.0	776.1	100 (>4.5 U/mL)	0	No fever	Heterozygous mutations (E148Q/L110P)

Note: Age, WBC, ESR, CRP, RF levels, and ACPA levels are given as mean±SD. Other values are given as median (range) or median (IQR).

ACPA: anti-cyclic citrullinated peptide antibodies, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, F: female, M: male, NA: not available, RF: rheumatoid factor, WBC: white blood cells

hibition is recognized as the best-validated biological intervention (16-19). Based on these findings, abatacept was deemed a safer and mechanistically unique alternative for addressing T-cell co-stimulation and adaptive immunological activation, whereas colchicine was retained for the management of the autoinflammatory aspect.

The episodic characteristics of monoarthritis may indicate a diagnosis of palindromic rheumatism, frequently regarded as a precursor to rheumatoid arthritis. The pronounced and constant reaction of these particular episodes to colchicine, together with the existence of *MEFV* variants, prompted us to contemplate a concurrent autoinflammatory process linked to the identified *MEFV* variants rather than solely palindromic rheumatism. This underscores the diagnostic difficulty in distinguishing these episodic arthritides, particularly in ACPA-positive individuals. Alternative etiologies of acute monoarthritis, including crystal-induced arthritis, were evaluated. Despite the absence of a synovial fluid analysis, the migratory pattern of arthritis, the lack of characteristic radiographic evidence for chondrocalcinosis, and the swift response to colchicine instead of NSAIDs rendered crystal-induced arthritis in this case as improbable.

A case-control study revealed a significant incidence of ACPA and elevated antibody titers among FMF subjects with arthritis (5). On the other hand, several other studies have reported no ACPA in any case and no differences in antibody levels between control groups and patients, irrespective of the presence of arthritis (8, 10, 11). However, in studies that included cases with positive ACPA, the overall positivity rate was only approximately 14%, indicating that ACPA is uncommon in FMF (5, 7). Studies detailing these cases were conducted in Turkey, and evidence regarding the prevalence of ACPA in FMF in Japan is lacking. FMF has been documented to coexist with other rheumatic disorders (3), and previous studies have indicated the potential coexistence of FMF and RA (4, 9, 12). Nonetheless, in the present instance, despite the initially elevated levels of RF and ACPA, no indications of arthritis were detected throughout the follow-up period. This unusual progression poses a problem for clinical assessment. In our case, colchicine was administered as a rescue therapy for pain and proved to be highly effective, leading us to conduct a *MEFV* gene analysis and identify heterozygous variants at L110P and E148Q. The diagnosis of FMF was deemed to fulfill the minor criteria of the Tel-Hashomer criteria established by Livneh et al. (20) and the diagnostic criteria of the Eurofever/PRINTO criteria (21), which encompass genetic abnormalities. According to the Tel-Hashomer criteria, our patient was categorized as having an "incomplete attack" phenotype. The patient met one minor criterion: recurrent monoarthritis that was responsive to colchicine. The attacks were deemed to be "incomplete" due to their afebrile nature and short duration (1-2 days). The patient satisfied the Eurofever/PRINTO requirements owing to the presence of a suitable *MEFV* gene variant in conjunction with colchicine effectiveness and a short attack duration.

The E148Q variant in exon 2 is the predominant variant of unknown significance (VUS), and recent guidelines have indicated that heterozygous E148Q variants do not support a diagnosis of FMF (1). In contrast, L110P is a variant located in exon 2 which has been identified in both Turkish and Spanish patients with FMF (22). A surveillance study of FMF gene variants in Japanese patients revealed that E148 Q-L110P variants were present in 5.6% of the subjects (23). Concerning the E148Q-L110P gene variants and their clinical manifestations, 50% of patients with FMF possessing these variants exhibited either no fever or only slight fever. Moreover, only 16.7% of the patients exhibit arthritis (24). A study examining the characteristics of FMF patients with multiple VUS variants revealed that, in contrast to patients with a single VUS variant, those with multiple VUS variants exhibited markedly lower responsiveness to colchicine treatment (88.9% vs. 96.7%; p=0.037). Furthermore, the presence of multiple VUS variants was significantly and independently correlated with colchicine resistance (odds ratio, 4.42; 95% confidence interval 1.08-18.1; p=0.038) (25). This study indicated a statistical tendency; however, not all people with multiple VUSs exhibited colchicine resistance. The favorable response in our patient, whose phenotype was defined by afebrile transient monoarthritis, may be ascribed to her specific L110P-E148Q genotype, which may not present the same resistance risk as other VUSs. Migita et al. categorized FMF into typical and atypical types according to the Tel-Hashomer criteria. Typical FMF patients display episodes of common symptoms, such as peritonitis, pleuritis, monoarticular arthritis, or fever, as defined by the Tel-Hashomer criteria. In contrast, atypical FMF patients show "incomplete" attacks. An episode is considered to be incomplete if it differs from the definition of a typical episode in one or two of the following characteristics: body temperature below 38°C; episode duration either shorter than 12 hours or longer than 3 days, but not shorter than 6 hours or exceeding one week; absence of peritonitis signs during abdominal episodes or localized signs; or atypical distribution of arthritis (26). Table 3 shows the characteristics of typical and atypical FMF (20, 26). The classification of this case as having an "atypical" phenotype, as delineated by these criteria, was predicated on these characteristics, with the symptoms of the episodes (afebrile, short-duration monoarthritis) also deemed to be atypical in comparison to classic FMF presentations. Although several studies have indicated that the E148Q-L110P genotype may correlate with a milder phenotype, including the absence of fever (24), the pathogenic implications of these variants, especially E148Q, are still controversial. Therefore, these genetic findings must be regarded with caution as possible factors contributing to an autoinflammatory tendency rather than as primary causes.

RA and FMF are categorized as autoimmune and autoinflammatory diseases, respectively, but they share a common underlying mechanism characterized by aberrant activation of the innate immune system via the inflammasome. In both conditions, the overproduction of IL-1β through the activa-

Table 3. Comparison of Typical and Atypical Cases of FMF.

		Typical FMF	Atypical FMF
Fever	Duration	12–72 hours	Within a few hours or lasting more than 4 days
	Temperature	≥38°C	Sometimes <38°C
Serositis		Non-localized	Localized
		Common	Less common
Arthritis	Monoarthritis	Polyarthritis	
Myalgia (ratio)		Low	High
***MEFV* mutations**		exon 10 (M694I)	exon 1 (E84K) exon 2 (E148Q, E148Q-L110P) exon 3 (P369S-R408Q) exon 5 (S503C)

FMF: familial Mediterranean fever

tion of Nod-like receptor protein 3 (NLRP3) or pyrin inflammasome is an important factor contributing to pathophysiology (27). The NLRP3 activation pathway induced by ACPA in RA (involving integrin, Panx-1, and two-pore domain weak inwardly rectifying K+ channel 2) and the regulatory mechanism of the pyrin inflammasome in FMF share the characteristic that the cytoskeleton (microtubules) and ion channels are crucial for signal transduction (28). Colchicine, an FMF medication, inhibits the pyroptosis inflammasome through RhoA signaling, highlighting the critical role of cytoskeletal dynamics in regulating inflammasome activity. The signal transduction of ACPA in RA is mediated by integrin, a cell adhesion protein, and is associated with cytoskeletal remodeling, suggesting the potential presence of analogous mechanisms in the signal transduction pathways of both diseases (28, 29). Clarifying the mechanisms by which ACPA stimulates the NLRP3 inflammasome will enhance our understanding of the RA etiology and emphasize its contributions to FMF, an autoinflammatory disease. These findings may facilitate the identification of shared therapeutic targets for both diseases and the formulation of novel treatment methods.

Conclusion

This case illustrates an uncommon case of a patient with positive results for ACPA and RF, who advanced to RA following a course of colchicine-responsive recurrent arthritis associated with *MEFV* variants. In patients with ACPA-positive arthralgia, the presence of symptoms atypical for RA, such as intermittent or migratory arthritis, necessitates caution when diagnosing RA. Differentiation from autoinflammatory diseases, particularly through *MEFV* gene testing, should therefore be performed. The clinical progression in this case substantiates the concept that autoimmune mechanisms in RA and autoinflammatory processes in FMF may interact via a shared pathophysiological foundation involving inflammasome activation. Instances of coexisting FMF and RA are uncommon, and treatment protocols for such patients are currently lacking. Elucidating the link between these two entities, currently categorized as distinct diseases, will enhance our understanding of the pathophysiology involved and may facilitate in the identification of novel therapeutic targets in the future.

The authors state that they have no Conflict of Interest (COI).

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Kazuhiro Itoh: conceptualization, data curation, writing - original draft, writing - review, and editing. Hiroshi Tsutani: writing-original draft, writing - review, and editing. Atsushi Kuwata: data curation, writing, reviewing, and editing. Nozomi Otsuki: data curation, writing, reviewing, and editing. Chiyo Kiriba: data curation, writing, review, and editing. Yoshimasa Urasaki: data curation, writing, reviewing, and editing. Masamichi Ikawa: data curation, writing, reviewing, and editing. Hiromichi Iwasaki: conceptualization, writing - original draft, writing - review and editing, supervision. Yasuhiko Mitsuke: writing, reviewed, edited, and supervised the study.

Data availability

Data are available upon reasonable request.

Declarations

This work was performed in accordance with the Declaration of Helsinki and its amendments and the Ethical Guidelines for Clinical Research from the Ministry of Health, Labour and Welfare, Japan. Written informed consent for the publication of this case report and genetic analysis was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

References

1. Romano M, Piskin D, Kul Cinar O, Sag E. Familial Mediterranean Fever; Recent Advances, Future Prospectives. Diagnostics (Basel) **15**: 813, 2025.

2. Jamilloux Y, Magnotti F, Belot A, Henry T. The pyrin inflammasome: from sensing RhoA GTPases-inhibiting toxins to triggering autoinflammatory syndromes. Pathog Dis **76**: 2018.

3. Migita K, Izumi Y, Jiuchi Y, Iwanaga N, Kawahara C, Agematsu K, et al. Familial Mediterranean fever is no longer a rare disease in Japan. Arthritis Res Ther **18**: 175, 2016.

4. Yago T, Asano T, Fujita Y, Migita K. Familial Mediterranean fever phenotype progression into anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis:a case report. Fukushima J Med Sci **66**: 160-6, 2020.

5. Uyanik A, Albayrak F, Uyanik MH, Dursun H, Keles M, Cetinkaya R. Antibodies directed to cyclic citrullinated peptides in familial Mediterranean fever. Rheumatol Int **30**: 467-71, 2010.

6. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis **69**: 1580-8, 2010.

7. Ceri M, Unverdi S, Altay M, Ureten K, Oztürk MA, Gönen N, et al. Anti-cyclic citrullinated peptides positivity rate in patients with familial Mediterranean fever. Clin Exp Rheumatol **28**: S58-61, 2010.

8. Karatay S, Yildirim K, Erdal A, Uzkeser H, Erdem FH, Yanmaz V. Anti-cyclic citrullinated peptide antibodies are not associated with familial Mediterranean fever. J Back Musculoskelet Rehabil **23**: 21-3, 2010.

9. Turan Y, Şendur ÖF, Berkit IK. Coexistence of Familial Mediterranean Fever and Rheumatoid Arthritis in A Case. Arch Rheumatol **25**: 044-6, 2010.

10. Guler E, Kaptanoglu E, Sahin O, Candan F, Hayta E, Elden H. Autoantibodies are not associated with familial mediterranean fever. Acta Reumatol Port **37**: 144-8, 2012.

11. Onur H, Aral H, Arica V, Bercem G, Usta M, Kasapcopur O. Anti-CCP Antibodies Are Not Associated with Familial Mediterranean Fever in Childhood. Int J Rheumatol **2013**: 498581, 2013.

12. Migita K, Abiru S, Sasaki O, Miyashita T, Izumi Y, Nishino A, et al. Coexistence of familial Mediterranean fever and rheumatoid arthritis. Mod Rheumatol **24**: 212-6, 2014.

13. Di Donato G, d'Angelo DM, Breda L, Chiarelli F. Monogenic Autoinflammatory Diseases: State of the Art and Future Perspectives. Int J Mol Sci **22**: 6360, 2021.

14. Cantarini L, Lopalco G, Vitale A, Coladonato L, Rigante D, Lucherini OM, et al. Paradoxical mucocutaneous flare in a case of Behçet's disease treated with tocilizumab. Clin Rheumatol **34**: 1141-3, 2015.

15. Wendling D, Prati C. Paradoxical effects of anti-TNF-α agents in inflammatory diseases. Expert Rev Clin Immunol **10**: 159-69, 2014.

16. Hentgen V, Vinit C, Fayand A, Georgin-Lavialle S. The Use of Interleukine-1 Inhibitors in Familial Mediterranean Fever Patients: A Narrative Review. Front Immunol **11**: 971, 2020.

17. Soriano A, Verecchia E, Afeltra A, Landolfi R, Manna R. IL-1β biological treatment of familial Mediterranean fever. Clin Rev Allergy Immunol **45**: 117-30, 2013.

18. Di Donato G, d'Angelo DM, Breda L, Chiarelli F. Monogenic Autoinflammatory Diseases: State of the Art and Future Perspectives. Int J Mol Sci **22**: 6360, 2021.

19. Chaaban A, Yassine H, Hammoud R, Kanaan R, Karam L, Ibrahim JN. A narrative review on the role of cytokines in the pathogenesis and treatment of familial Mediterranean fever: an emphasis on pediatric cases. Front Pediatr **12**: 1421353, 2024.

20. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum **40**: 1879-85, 1997.

21. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis **78**: 1025-32, 2019.

22. Domingo C, Touitou I, Bayou A, Ozen S, Notarnicola C, Dewalle M, et al. Familial Mediterranean fever in the 'Chuetas' of Mallorca: a question of Jewish origin or genetic heterogeneity. Eur J Hum Genet **8**: 242-6, 2000.

23. Migita K, Uehara R, Nakamura Y, Yasunami M, Tsuchiya-Suzuki A, Yazaki M, et al. Familial Mediterranean fever in Japan. Medicine (Baltimore) **91**: 337-43, 2012.

24. Kishida D, Nakamura A, Yazaki M, Tsuchiya-Suzuki A, Matsuda M, Ikeda S. Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. Arthritis Res Ther **16**: 439, 2014.

25. Kishida D, Yazaki M, Nakamura A, Tsuchiya-Suzuki A, Ichikawa T, Shimojima Y, et al. Impact of multiple MEFV variants of unknown significance on the diagnosis and clinical presentation of familial Mediterranean fever. Immunol Med **47**: 186-91, 2024.

26. Migita K, Agematsu K, Yazaki M, Nonaka F, Nakamura A, Toma T, et al. Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients. Medicine (Baltimore) **93**: 158-64, 2014.

27. Dong X, Zheng Z, Lin P, Fu X, Li F, Jiang J, et al. ACPAs promote IL-1β production in rheumatoid arthritis by activating the NLRP3 inflammasome. Cell Mol Immunol **17**: 261-71, 2020.

28. Cai L, Zhang K, Gao J, Xiao B, Li M, Meng X, et al. ACPA-Induced ATP release and K+ efflux trigger NLRP3 inflammasome activation in rheumatoid arthritis. Cell Commun Signal **23**: 302, 2025.

29. Özen S, Batu ED, Demir S. Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management. Front Immunol **8**: 253, 2017.

frontiers in Cellular and Infection Microbiology

TYPE Opinion
PUBLISHED 24 March 2026
DOI 10.3389/fcimb.2026.1798936

OPEN ACCESS

EDITED BY
Ana Gonçalves Domingos,
New University of Lisbon, Portugal

REVIEWED BY
Alexey V. Rakov,
Central Research Institute of Epidemiology (CRIE), Russia
Lorena Rodriguez-Munoz,
Hospital del Niño, Mexico

*CORRESPONDENCE
Kazuhiro Itoh
kitoh@u-fukui.ac.jp

RECEIVED 29 January 2026
REVISED 04 March 2026
ACCEPTED 11 March 2026
PUBLISHED 24 March 2026

CITATION
Itoh K, Tsutani H, Mitsuke Y, Ikawa M and Iwasaki H (2026) A new therapeutic strategy for spotted fever group rickettsioses: a proposal for evaluating combination therapy with tetracycline and fluoroquinolones. *Front. Cell. Infect. Microbiol.* 16:1798936. doi: 10.3389/fcimb.2026.1798936

A new therapeutic strategy for spotted fever group rickettsioses: a proposal for evaluating combination therapy with tetracycline and fluoroquinolones

Kazuhiro Itoh [1,2*], Hiroshi Tsutani[1], Yasuhiko Mitsuke[1], Masamichi Ikawa[2] and Hiromichi Iwasaki[2]

[1]Department of Internal Medicine, NHO Awara National Hospital, Awara, Japan, [2]Department of Community Health Science, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

KEYWORDS
fluoroquinolone, Japanese spotted fever, Rocky Mountain spotted fever, spotted fever group rickettsioses, tetracycline

Introduction

Spotted fever group rickettsioses (SFGR) are significant tick-borne diseases worldwide, attributed to various *Rickettsia* species (Blanton, 2019; Zhang et al., 2023). Even though the clinical signs are similar, the death rates are very different depending on the pathogen and the patient's risk factors. In tropical and subtropical areas, such as Africa, the Mediterranean, and Brazil, tick-bite fever, Mediterranean spotted fever (MSF), and the highly lethal Brazilian spotted fever are all very common (Angerami et al., 2006; Bechah et al., 2012).

The Centers for Disease Control and Prevention (CDC) says that tetracycline antibiotics (such as doxycycline) should be given right away as the main treatment (CDC, 2025). Even with this standard of care, the death rate for severe SFGR, like Rocky Mountain spotted fever (RMSF), is still too high (5–10%) (Jay and Armstrong, 2020), showing how badly novel strategies are needed.

Insights derived from Japanese spotted fever (JSF), induced by *Rickettsia japonica*, may be crucial. A retrospective analysis demonstrated that the combination of tetracycline and a fluoroquinolone considerably decreased the duration of fever in comparison to tetracycline alone (Itoh et al., 2023). Due to the common Toll-like receptor 4 (TLR4)-mediated immune responses in SFGR (Rumfield et al., 2020; Voss et al., 2021), this efficacy may be translatable. This study combines clinical and molecular knowledge to put out a therapeutic hypothesis: that using tetracyclines and fluoroquinolones together is an effective way to treat severe SFGR.

Common pathophysiology of spotted fever group rickettsioses

The pathogenesis of SFGR is driven by the replication of rickettsiae within vascular endothelial cells (Clifton et al., 2005). When the endothelium is injured, it becomes more permeable. This leads to edema, hypotension, and the characteristic rash associated with the illness (Jay and Armstrong, 2020). In severe instances, disseminated intravascular coagulation (DIC) and multiple organ failure may occur.

The immunological response initiates upon the detection of rickettsial lipopolysaccharide (LPS) by the TLR4/MD2 complex (Maeshima and Fernandez, 2013; Guillotte et al., 2018). This turns on the NF-κB pathway, which causes the release of inflammatory cytokines such as IL-1β, IL-8, and MCP-1 (Clifton et al., 2005; Rumfield et al., 2020). Dysregulated synthesis of these mediators, essential for defense, might precipitate a "cytokine storm," resulting in fatal consequences (Karki and Kanneganti, 2021). This TLR4-dependent mechanism is common in SFGR, which makes it important to target this pathway for treatment. Table 1 shows a comparison of the most important features of the major SFGR.

Foundational evidence from Japanese spotted fever

JSF, a type of SFGR caused by *R. japonica* that can make you very sick, is an important clinical model for studying how well combination therapy might work (Itoh et al., 2023). In severe cases of JSF, disseminated intravascular coagulation and multiple organ failure may ensue, resulting in fatal outcomes, with a recorded death incidence of roughly 4.1% in 2019 (Itoh et al., 2023).

Several case reports have demonstrated the efficacy of combining tetracycline and fluoroquinolone antibiotics for severe JSF; however, our retrospective study employing a mixed-effects model yielded robust quantitative results. The study demonstrated that the combination therapy group exhibited a significantly greater reduction in body temperature compared to the tetracycline monotherapy group on both day 3 (difference: –0.569 °C; 95% CI: –1.117 to –0.020; p = 0.042) and day 4 (difference: –0.628 °C; 95% CI: –1.184 to –0.073; p = 0.027) of treatment (Itoh et al., 2023). The combination therapy shortened the duration to defervescence by 1.5 days, a key measure for quantitatively evaluating treatment effectiveness in infectious illnesses (Itoh et al., 2024a).

However, the safety profile of this combination requires careful interpretation. While two retrospective database studies in Japan did not show a mortality benefit for the combination, one study indicated a potential risk of convulsions and higher mortality (Kutsuna et al., 2022; Yasuda et al., 2024). A granular analysis of these results, however, uncovers significant subtleties. The correlation with negative outcomes in the study conducted by Yasuda et al. was predominantly influenced by cases related to ciprofloxacin. Importantly, levofloxacin, which made up the majority of combination therapy cases (87.0%), did not lead to higher death rates or serious problems compared to tetracycline monotherapy (Yasuda et al., 2024). This suggests that the reported risks may be drug-specific—potentially linked to ciprofloxacin-induced toxin upregulation or interactions—rather than a class effect of fluoroquinolones when used in combination. Importantly, given that levofloxacin represented the vast majority of the combination group in our efficacy analysis as well, the significant reduction in fever duration (1.5 days) is effectively a demonstration of the clinical benefit of the tetracycline-levofloxacin regimen.

Moreover, it is imperative to confront a significant issue frequently highlighted in previous literature about the application of fluoroquinolones for rickettsioses. Botelho-Nevers et al. conducted a well referenced retrospective analysis on Mediterranean spotted fever (MSF), revealing that fluoroquinolone treatment was independently linked to heightened illness severity (Botelho-Nevers et al., 2011). It is essential to highlight that this study assessed fluoroquinolone monotherapy in comparison to standard tetracycline therapy. The

TABLE 1 Key characteristics of major spotted fever group rickettsioses (SFGR) and implications for combination therapy.

Feature	Rocky Mountain spotted fever	Japanese spotted fever	Implications for SFGR
Causative organism	*R. rickettsii*	*R. japonica*	Multiple *Rickettsia* spp. worldwide
Geography	USA, Latin America; high fatality in Brazil/Mexico	Japan, East Asia	Distribution expanding in tropical/subtropical regions
Mortality	5–10%; ≥30% if delayed	~4.1%	Severity driven by endothelial injury & cytokine storm
Pathophysiology	Endothelial infection → vasculitis	Same	Shared TLR4/NF-κB/MAPK pathways
Standard therapy	Doxycycline	Doxycycline/minocycline	Early tetracycline is essential
Combination therapy evidence	Limited	In retrospective case series, combination with fluoroquinolone shortened fever by ~1.5 days	Hypothesis-generating for severe SFGR
Mechanistic rationale	—	Dual blockade (FQ = upstream; TC = downstream)	Additive inhibition of TLR4 signaling demonstrated in THP-1 *in vitro*
Precautions	FQ concerns in MSF (*R. conorii*)	—	Pathogen differentiation crucial in co-endemic scrub typhus regions

FQ, fluoroquinolone; MAPK, mitogen-activated protein kinase; MSF, Mediterranean spotted fever; NF-κB, nuclear factor kappa B; SFGR, spotted fever group rickettsioses; TC, tetracycline; TLR4, Toll-like receptor 4.

adverse results presumably stemmed from the suboptimal rickettsicidal efficacy of fluoroquinolones, resulting in treatment failure, rather than a toxic synergy intrinsic to the medication class. Although a subsequent *in vitro* study suggested that ciprofloxacin may upregulate a toxin-antitoxin module in *R. conorii* (Botelho-Nevers et al., 2012), this effect has not been shown to adversely affect outcomes when a potent rickettsicidal agent such as doxycycline is simultaneously administered, as indicated by the safety of the levofloxacin combination in JSF data. Therefore, our proposal endorses combination therapy (tetracycline + fluoroquinolone) to exploit the immunomodulatory advantage, solely as an adjuvant to tetracyclines, and evidence of monotherapy failure should not inhibit this strategy.

Nevertheless, given the nuances in safety data, a prospective randomized controlled trial is necessary to definitively evaluate the advantages and disadvantages of this combination therapy, ideally utilizing levofloxacin, which has demonstrated both safety and potential efficacy in retrospective analyses. The findings supporting expedited fever control in JSF offer a noteworthy clinical justification for advocating this immunomodulatory strategy for other severe SFGR.

Mechanism of action: a dual immunomodulatory strategy

Although both tetracyclines and fluoroquinolones exhibit direct anti-rickettsial activity (Rolain et al., 1998; Satoh et al., 2019), the principal benefit of their concurrent application likely arises from their complementary immunomodulatory effects, which surpass their antibacterial capabilities. This approach fundamentally involves the simultaneous inhibition of the TLR4 signaling pathway, which is triggered by rickettsial LPS (Guillotte et al., 2018; Rumfield et al., 2020; Voss et al., 2021) (Figure 1).

These two groups of drugs regulate the host immune response through unique and complementary mechanisms.

1. Fluoroquinolones, including ciprofloxacin and levofloxacin, prevent the inflammatory cascade from taking place. They inhibit the first attachment of LPS to the TLR4/MD2 receptor complex on the surface of the host's immune cells (Zusso et al., 2019). By obstructing this initial phase, they impede the subsequent signaling cascade, resulting in a reduction of inflammatory cytokines such as TNF-α and IL-1β in microglia and macrophage models (Zusso et al., 2019).

2. Tetracyclines, including minocycline and doxycycline, function inside cells and further down the signaling pathway. This is distinct from how other drugs work. They inhibit the phosphorylation of IκB kinase (IKK) α/β, which is the first step in starting the pro-inflammatory transcription factor NF-κB (Cazalis et al., 2008; Tai et al., 2013). By preventing NF-κB from being activated, they greatly reduce the production of many inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, IL-8, and MCP-1 (Cazalis et al., 2008; Tai et al., 2013).

The concurrent inhibition of both the upstream trigger (receptor binding) and the downstream signaling (intracellular transduction) by the combination of tetracycline and fluoroquinolone is hypothesized to produce a more extensive and potent suppression of the inflammatory response than either agent individually. Recent *in vitro* findings by Sakamaki et al. substantiate this hypothesis, demonstrating that the combination of minocycline and ciprofloxacin significantly enhances the inhibitory effect on TNF-α production and reduces inflammatory chemokines (IL-8, IP-10) in LPS-stimulated THP-1 monocytic cells, surpassing the effects of either drug alone (Sakamaki et al., 2025). This dual blocking is the proposed mechanism to avert the life-threatening cytokine storm and mitigate the significant vascular endothelial damage linked to advanced SFGR (Karki and Kanneganti, 2021).

Discussion

Our opinion is that tetracycline–fluoroquinolone (TC+FQ) combination therapy merits formal evaluation as an adjunctive strategy for severe or high-risk SFGR. This hypothesis-driven approach is grounded in dual immunomodulatory blockade of the TLR4 pathway and supportive retrospective observations in JSF. However, translating this concept into feasible trials and responsible clinical use requires explicit operational plans for safety, target population, and a key diagnostic confounder: scrub typhus.

Operationalizing the scrub typhus confounder in trials and practice

Because *Orientia tsutsugamushi* is intrinsically fluoroquinolone-resistant and rapid point-of-care diagnostics distinguishing SFGR from scrub typhus are not widely available in many endemic settings, enrollment and treatment algorithms must be designed for real-world constraints rather than assuming immediate microbiologic confirmation. Importantly, we do not assume that all SFGR share identical clinical features with JSF, nor do we propose extrapolating JSF-specific findings as universal rules for SFGR. Instead, we propose a pragmatic "enrichment + safety-switch" framework that can be adapted to local epidemiology and locally prevalent SFGR species.

First, clinical–epidemiologic enrichment should be region- and species-informed. Rather than enrolling all undifferentiated febrile rash illnesses, trial eligibility can be restricted to patients whose presentation is most consistent with SFGR in the given setting and less consistent with scrub typhus, using pre-specified criteria informed by local surveillance data and published clinical patterns. In regions where JSF is the predominant SFGR, enrichment criteria may incorporate JSF-based differentiating features as illustrative, locally relevant examples (e.g., palm/sole involvement reported more frequently in JSF cohorts, relatively small or inconspicuous eschars, and region-specific seasonality), while explicitly acknowledging that other SFGR species may present

10.3389/fcimb.2026.1798936

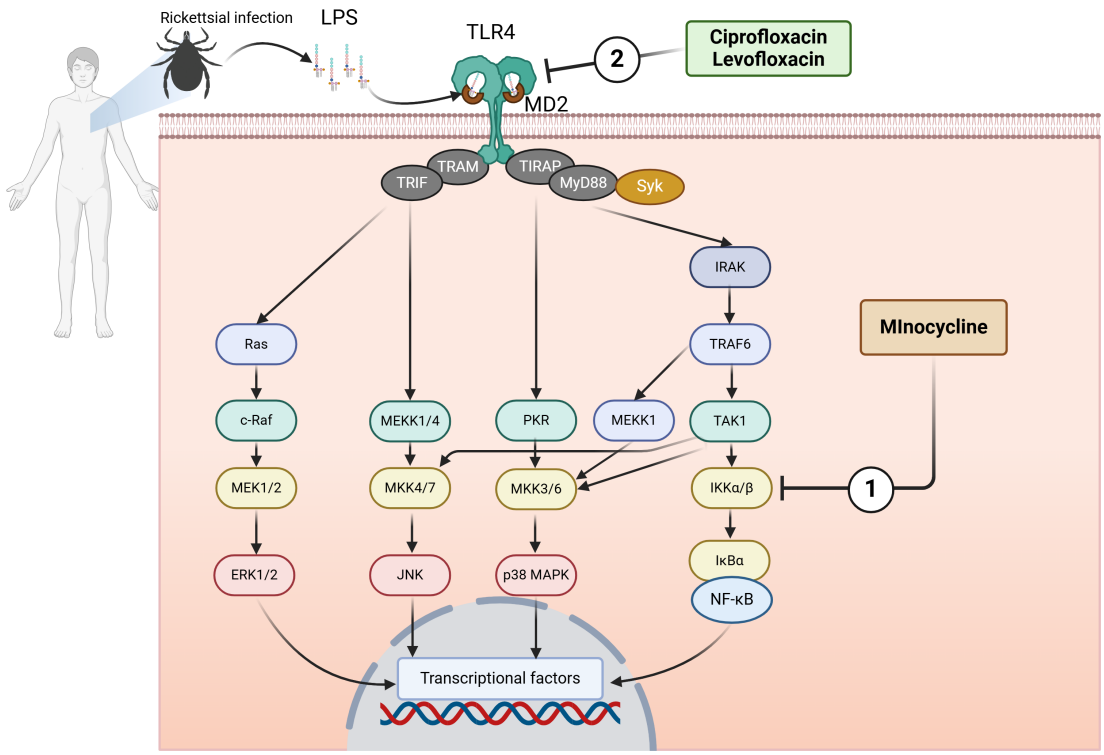


FIGURE 1
Dual immunomodulatory effects of tetracyclines and fluoroquinolones on TLR4 signaling in host immune cells. LPS from *Rickettsia* engages the TLR4/MD2 complex, leading to dimerization and activation of downstream signaling via NF-κB and MAPKs. 1) Minocycline inhibits phosphorylation of IKKα/β and prevents NF-κB activation, reducing TNF-α and chemokine production. 2) Ciprofloxacin and levofloxacin inhibit upstream LPS–TLR4/MD2 interaction and suppress phosphorylation of NF-κB p65 and ERK. Recent *in vitro* evidence shows that minocycline + ciprofloxacin produce additive inhibition of TNF-α, IL-8, IP-10, MIP-1α, and MIP-1β, and more strongly suppress NF-κB p65 activation than either drug alone in LPS-stimulated THP-1 cells. These findings support the concept of combined upstream and downstream blockade of the TLR4 pathway. ERK, extracellular signal-regulated kinase; IκBα, inhibitor of nuclear factor kappa-B kinase alpha; IKKα/β, IκB kinase alpha/beta; IL-8, interleukin-8; IP-10, interferon-inducible protein 10; IRAK, IL-1 receptor-related kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MEKK, mitogen-activated protein/ERK kinase kinase; MD2, myeloid differentiation factor 2; MIP-1α, macrophage inflammatory protein-1α; MKK, mitogen-activated protein kinase kinase; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa-B; PKR, double-stranded RNA-activated protein kinase; Syk, spleen tyrosine kinase; TAK1, transforming growth factor-β-activated kinase 1; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain-containing adaptor protein; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TRAF, tumor necrosis factor receptor associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor protein inducing interferon-β. The figure was created using BioRender (https://biorender.com/).

differently. In other geographic areas, enrichment criteria should be recalibrated to the dominant local SFGR species and their known clinical spectrum.

Second, mandatory confirmatory testing with a prespecified "rescue switch" is essential for safety. At enrollment, all participants should submit specimens for definitive testing (e.g., PCR from eschar/whole blood and/or paired serology). Because results may return after empiric therapy has started, the protocol should include a clear safety rule: if scrub typhus is confirmed—or becomes strongly suspected on follow-up based on evolving clinical features or available testing—the fluoroquinolone component must be discontinued immediately and patients should continue standard effective therapy, with predefined monitoring for clinical deterioration.

Third, analytic handling should be prespecified to preserve interpretability. Participants later confirmed as scrub typhus should be excluded from the per-protocol analysis and handled using a modified intention-to-treat (mITT) framework, complemented by sensitivity analyses using different case-definition thresholds. This ensures that pragmatic enrollment does not dilute efficacy estimates for SFGR while maintaining patient safety and transparency.

In short, we do not advocate empiric TC+FQ for all febrile rash illnesses. Rather, we propose a locally calibrated enrichment strategy coupled with mandatory confirmatory testing and an immediate fluoroquinolone discontinuation ("rescue switch") rule to operationalize the confounder in settings where point-of-care differentiation is limited. We emphasize that enrichment criteria are intended to increase pre-test probability, not to replace microbiologic diagnosis, and must be updated as local epidemiology and diagnostic availability evolve.

Who should be studied first

Because most uncomplicated SFGR respond to tetracycline alone, we propose evaluating TC+FQ primarily in severe/high-

risk SFGR (e.g., early organ dysfunction, DIC tendency, encephalopathy, hypotension). In this subgroup, accelerated control of hyperinflammation may plausibly translate into clinically meaningful stabilization. The regimen should remain anchored on an effective tetracycline, and the fluoroquinolone component should be selected with caution given drug-specific concerns reported for ciprofloxacin in other rickettsioses.

Safety oversight and feasibility

Future trials should incorporate structured safety monitoring (e.g., neurologic events, arrhythmia/QT risk where relevant), predefined stopping rules, and independent oversight. This framework allows the field to test the hypothesis responsibly while acknowledging diagnostic and operational realities in endemic regions.

Conclusion and future directions

Even though the *Rickettsia* species that cause SFGR (such as RMSF and JSF) are different, they all have very comparable TLR4-dependent host immune responses and clinical presentations (Blanton, 2019; Jay and Armstrong, 2020; Itoh et al., 2023). The CDC (CDC, 2025) says that tetracycline antibiotics are the best treatment, however the high death rate in severe SFGR cases demonstrates how desperately we need new options (Jay and Armstrong, 2020). This study integrates modern clinical and molecular findings to offer an innovative therapeutic approach: the combination of tetracycline and fluoroquinolone antibiotics. The justification for the proposal is twofold. Recent clinical findings from JSF suggest that this combination therapy can induce defervescence more effectively than tetracycline monotherapy (Itoh et al., 2023, Itoh et al, 2024b). We propose that this accelerated defervescence is not solely a symptomatic improvement (i.e., a more rapid alleviation of sickness behavior) but rather a clinical marker of earlier regulation of the underlying immunological hyperactivity. The efficacy of employing early clinical response, including defervescence, as a therapeutic endpoint is well-documented in other acute bacterial infections, such as community-acquired pneumonia, where it is applied in clinical trials sanctioned by regulatory authorities like the U.S. Food and Drug Administration (FDA) and in associated analyses (Laessig, 2010; U.S. Food and Drug Administration, 2020). Although our 1.5-day reduction necessitates prospective validation to establish a direct correlation with decreased mortality, we hypothesize that the timely management of hyperinflammation is the essential initial measure in averting the advancement to severe consequences, including DIC and organ failure. The significant immunomodulatory effect of this combination—attained by simultaneously inhibiting the TLR4 inflammatory pathway at both upstream and downstream sites—offers a robust molecular basis for its potential effectiveness (Cazalis et al., 2008; Tai et al., 2013; Zusso et al., 2019). This dual blockage may be key in preventing the lethal cytokine storm and mitigating the significant vascular endothelial damage that contributes to mortality in these conditions (Karki and Kanneganti, 2021).

Prior to conducting large-scale trials, preclinical investigations utilizing proven animal models of severe SFGR would be essential to further evaluate the *in vivo* efficacy and mechanisms of this combination therapy. Models like the virulent *Rickettsia parkeri* infection model in C3H/HeN mice or the endothelial-targeting *R. conorii* model might be appropriate for this objective (Bechah et al., 2012; Londoño et al., 2019). Due to their shared endemic areas, SFGR and scrub typhus (caused by *O. tsutsugamushi*) are difficult to diagnose in clinical practice (Sakamaki et al., 2025). This is important since *O. tsutsugamushi* has a gyrA (Ser83Leu) mutation that makes it fluoroquinolone-resistant (Jang et al., 2013). Clinical worsening has been observed in scrub typhus patients receiving ciprofloxacin treatment (Jang et al., 2013). Accordingly, operationalization should rely on a tiered approach (clinical pre-screening/enrichment, mandatory confirmatory testing with a prespecified rescue switch, and mITT/per-protocol analytic handling), as detailed in the Discussion section. Given the limitations of retrospective investigations, a prospective, carefully designed, and rigorously controlled randomized controlled trial (RCT) is needed to confirm this therapeutic approach (Kutsuna et al., 2022; Yasuda et al., 2024). Regulatory authorities (FDA, 2020) have stated that rigorous studies are required to determine the efficacy and safety of novel antibacterial treatments for severe infections. The trial should be structured to assess the efficacy and safety of combination therapy, specifically in SFGR patients classified as high risk for severe disease. Based on epidemiological risk factors for mortality, we define "high-risk" patients as those of advanced age, those with delayed initiation of treatment, or those presenting with early signs of organ dysfunction. As the majority of mild cases recover with standard care, this demographic represents the most urgent unmet need and necessitates a meticulous evaluation of the potential risk-benefit ratio of the combination, utilizing levofloxacin as the primary candidate. This signifies the subsequent crucial stage in improving results for those suffering from these challenging infections, and we firmly endorse the initiation of such clinical trials.

Author contributions

KI: Data curation, Writing – review & editing, Methodology, Writing – original draft, Formal analysis, Investigation, Software, Visualization, Resources, Conceptualization, Validation, Project administration. HT: Methodology, Formal analysis, Supervision, Writing – review & editing, Writing – original draft, Data curation, Conceptualization, Investigation, Project administration, Validation. YM: Project administration, Writing – review & editing, Methodology, Supervision, Validation, Investigation, Writing – original draft, Data curation, Formal analysis. MI:

Project administration, Data curation, Formal analysis, Validation, Methodology, Supervision, Writing – review & editing, Writing – original draft, Investigation, Conceptualization. HI: Validation, Methodology, Investigation, Supervision, Data curation, Writing – review & editing, Conceptualization, Project administration, Writing – original draft, Formal analysis.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

Angerami, R. N., Resende, M. R., Feltrin, A. F. C., Katz, G., Nascimento, E. M., Stucchi, R. S. B., et al. (2006). Brazilian spotted fever: a case series from an endemic area in southeastern Brazil: epidemiological aspects. *Ann. N Y Acad. Sci.* 1078, 170–172. doi: 10.1196/annals.1374.030

Bechah, Y., Mege, J.-L., and Raoult, D. (2012). Cross-protection among Rickettsia species and subspecies in a Guinea pig model of cutaneous infection. *Comp. Immunol. Microbiol. Infect. Dis.* 35, 551–556. doi: 10.1016/j.cimid.2012.06.002

Blanton, L. S. (2019). The rickettsioses: A practical update. *Infect. Dis. Clin. North Am.* 33, 213–229. doi: 10.1016/j.idc.2018.10.010

Botelho-Nevers, E., Edouard, S., Leroy, Q., and Raoult, D. (2012). Deleterious effect of ciprofloxacin on Rickettsia conorii-infected cells is linked to toxin-antitoxin module up-regulation. *J. Antimicrob. Chemother.* 67, 1677–1682. doi: 10.1093/jac/dks089

Botelho-Nevers, E., Rovery, C., Richet, H., and Raoult, D. (2011). Analysis of risk factors for Malignant Mediterranean spotted fever indicates that fluoroquinolone treatment has a deleterious effect. *J. Antimicrob. Chemother.* 66, 1821–1830. doi: 10.1093/jac/dkr218

Cazalis, J., Bodet, C., Gagnon, G., and Grenier, D. (2008). Doxycycline reduces lipopolysaccharide-induced inflammatory mediator secretion in macrophage and ex vivo human whole blood models. *J. Periodontol* 79, 1762–1768. doi: 10.1902/jop.2008.080051

Centers for Disease Control and Prevention (CDC) (2025). "Rickettsial diseases," in *Yellow book*. Atlanta, GA: Centers for Disease Control and Prevention Available online at: https://www.cdc.gov/yellow-book/hcp/travel-associated-infections-diseases/rickettsial-diseases.html.

Clifton, D. R., Rydkina, E., Huyck, H., Pryhuber, G., Freeman, R. S., Silverman, D. J., et al. (2005). Expression and secretion of chemotactic cytokines IL-8 and MCP-1 by human endothelial cells after Rickettsia rickettsii infection: regulation by nuclear transcription factor NF-kappaB. *Int. J. Med. Microbiol.* 295, 267–278. doi: 10.1016/j.ijmm.2005.05.006

Guillotte, M. L., Gillespie, J. J., Chandler, C. E., Rahman, M. S., Ernst, R. K., and Azad, A. F. (2018). Rickettsia lipid A biosynthesis utilizes the late acyltransferase lpxJ for secondary fatty acid addition. *J. Bacteriol* 200, e00334–e00318. doi: 10.1128/JB.00334-18

Itoh, K., Fukaya, K., Suzuki, Y., Kiriba, C., Kuwata, A., Otsuki, N., et al. (2024a). Administration and comparison of tetracycline alone and tetracycline combined with fluoroquinolone therapy in two cases of Japanese spotted fever with different treatment strategies (in Japanese). *Jpn J. Hosp Gen. Med.* 20, 295–300. doi: 10.60227/jhgmwabun.20.5_295

Itoh, K., Kabata, D., Shigemi, H., Hirota, T., Sakamaki, I., Tsutani, H., et al. (2023). Evaluation of tetracycline and fluoroquinolone therapy against Japanese spotted fever: Analysis based on individual data from case reports and case series. *Int. J. Antimicrob. Agents* 62, 106895. doi: 10.1016/j.ijantimicag.2023.106895

Itoh, K., Kabata, D., Shigemi, H., Hirota, T., Sakamaki, I., Tsutani, H., et al. (2024b). In reply to the Letter to Editor regarding "Evaluation of tetracycline and fluoroquinolone therapy against Japanese spotted fever: Analysis based on individual data from case reports and case series. *Int. J. Antimicrob. Agents* 64, 107246. doi: 10.1016/j.ijantimicag.2024.107246

Jang, H.-C., Choi, S.-M., Jang, M.-O., Ahn, J.-H., Kim, U.-J., Kang, S.-J., et al. (2013). Inappropriateness of quinolone in scrub typhus treatment due to gyrA mutation in Orientia tsutsugamushi Boryong strain. *J. Korean Med. Sci.* 28, 667–671. doi: 10.3346/jkms.2013.28.5.667

Jay, R., and Armstrong, P. A. (2020). Clinical characteristics of Rocky Mountain spotted fever in the United States: A literature review. *J. Vector Borne Dis.* 57, 114–120. doi: 10.4103/0972-9062.310863

Karki, R., and Kanneganti, T.-D. (2021). The "cytokine storm": molecular mechanisms and therapeutic prospects. *Trends Immunol.* 42, 681–705. doi: 10.1016/j.it.2021.06.001

Kutsuna, S., Ohbe, H., Matsui, H., and Yasunaga, H. (2022). Effectiveness of fluoroquinolone antimicrobials in addition to tetracyclines for Japanese spotted fever: A retrospective analysis using a national inpatient database. *Int. J. Infect. Dis.* 123, 70–75. doi: 10.1016/j.ijid.2022.08.006

Laessig, K. A. (2010). End points in hospital-acquired pneumonia and/or ventilator-associated pneumonia clinical trials: food and drug administration perspective. *Clin. Infect. Dis.* 51 Suppl 1, S117–S119. doi: 10.1086/653059

Londoño, A. F., Mendell, N. L., Walker, D. H., and Bouyer, D. H. (2019). A biosafety level-2 dose-dependent lethal mouse model of spotted fever rickettsiosis: Rickettsia parkeri Atlantic Rainforest strain. *PloS Negl. Trop. Dis.* 13, e0007054. doi: 10.1371/journal.pntd.0007054

Maeshima, N., and Fernandez, R. C. (2013). Recognition of lipid A variants by the TLR4-MD-2 receptor complex. *Front. Cell Infect. Microbiol.* 3. doi: 10.3389/fcimb.2013.00003

Rolain, J. M., Maurin, M., Vestris, G., and Raoult, D. (1998). *In vitro* susceptibilities of 27 rickettsiae to 13 antimicrobials. *Antimicrob. Agents Chemother.* 42, 1537–1541. doi: 10.1128/AAC.42.7.1537

Rumfield, C., Hyseni, I., McBride, J. W., Walker, D. H., and Fang, R. (2020). Activation of ASC inflammasome driven by toll-like receptor 4 contributes to host immunity against rickettsial infection. *Infect. Immun.* 88, e00886–e00819. doi: 10.1128/IAI.00886-19

Sakamaki, I., Tanaka, Y., and Iwasaki, H. (2025). Combination of minocycline and ciprofloxacin enhances the inhibitory effect of Tumor necrosis factor alpha production in lipopolysaccharide-stimulated THP-1 monocytic cells. *Infect. Med.* 100214. doi: 10.1016/j.imj.2025.100214

Satoh, M., Kato, H., Takayama-Ito, M., Ogawa, M., Ando, S., and Saijo, M. (2019). *In vitro* evaluation of minimum inhibitory concentration of several antibacterial agents

against Rickettsia japonica using a plaque reduction assay system. *J. Infect. Chemother.* 25, 917–919. doi: 10.1016/j.jiac.2019.05.019

Tai, K., Iwasaki, H., Ikegaya, S., and Ueda, T. (2013). Minocycline modulates cytokine and chemokine production in lipopolysaccharide-stimulated THP-1 monocytic cells by inhibiting IκB kinase α/β phosphorylation. *Transl. Res.* 161, 99–109. doi: 10.1016/j.trsl.2012.10.001

U.S. Food and Drug Administration (2020). *Community-acquired bacterial pneumonia: developing drugs for treatment*. Available online at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/community-acquired-bacterial-pneumonia-developing-drugs-treatment (Accessed November 15, 2025).

Voss, O. H., Cobb, J., Gaytan, H., Rivera Díaz, N., Sanchez, R., DeTolla, L., et al. (2021). Pathogenic, but Not Nonpathogenic, Rickettsia spp. Evade Inflammasome-Dependent IL-1 Responses To Establish an Intracytosolic Replication Niche. *mBio* 13, e0291821. doi: 10.1128/mbio.02918-21

Yasuda, I., Toizumi, M., and Sando, E. (2024). Deleterious effects of a combination therapy using fluoroquinolones and tetracyclines for the treatment of Japanese spotted fever: a retrospective cohort study based on a Japanese hospital database. *J. Antimicrob. Chemother.* 79, 1962–8. doi: 10.1093/jac/dkae192

Zhang, Y.-Y., Sun, Y.-Q., Chen, J.-J., Teng, A.-Y., Wang, T., Li, H., et al. (2023). Mapping the global distribution of spotted fever group rickettsiae: a systematic review with modelling analysis. *Lancet Digit Health* 5, e5–e15. doi: 10.1016/S2589-7500(22)00212-6

Zusso, M., Lunardi, V., Franceschini, D., Pagetta, A., Lo, R., Stifani, S., et al. (2019). Ciprofloxacin and levofloxacin attenuate microglia inflammatory response via TLR4/NF-kB pathway. *J. Neuroinflamm.* 16, 148. doi: 10.1186/s12974-019-1538-9