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Type I Interferon in Children with Viral or Bacterial Infections

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BACKGROUND: Fever is one of the leading causes of consultation in the pediatric emergency department for patients under the age of 3 years. Distinguishing between bacterial and viral infections etiologies in febrile patients remains challenging. We hypothesized that specific host biomarkers for viral infections, such as type I-interferon (IFN), could help clinicians' decisions and limit antibiotic overuse.

METHODS: Paxgene tubes and serum were collected from febrile children (n = 101), age from 7 days to 36 months, with proven viral or bacterial infections, being treated at pediatric emergency departments in France. We assessed the performance of an IFN signature, which was based on quantification of expression of IFN-stimulated genes using the Nanostring® technology and plasma IFN-α quantified by digital ELISA technology.

RESULTS: Serum concentrations of IFN-α were below the quantification threshold (30 fg/mL) for 2% (1/46) of children with proven viral infections and for 71% (39/55) of children with bacterial infections ($P < 0.001$). IFN-α concentrations and IFN score were significantly higher in viral compared to bacterial infection ($P < 0.001$). There was a strong correlation between serum IFN-α concentrations and IFN score (p-pearson = 0.83). Both serum IFN-α concentration and IFN score robustly discriminated (Area Under the Curve >0.91 for both) between viral and bacterial infection in febrile children, compared to C-reactive protein (0.83).

CONCLUSIONS: IFN-α is increased in blood of febrile infants with viral infections. The discriminative performance of IFN-α femtomolar concentrations as well as blood transcriptional signatures could show a diagnostic benefit and potentially limit antibiotic overuse.

CLINICAL TRIALS REGISTRATION: clinicaltrials.gov (NCT03163628).

Type I interferons (IFNs) are a group of cytokines that are involved in the innate antiviral response. A chronic exposure to these cytokines is also linked to the pathophysiology of a group of autoimmune diseases called type I interferonopathies *(1, 2)*. Because IFNs are secreted at very low concentrations (femtomolar) during disease course, detection of type I IFN in patients remains challenging and has led several groups to propose an alternative strategy for the monitoring of this group of cytokines. Based on the quantification of expression of IFN-stimulated genes (ISGs), blood transcriptional signatures (IFN signatures) provide an indirect estimate of the exposure of cells to type I IFN and are being proposed for the screening of autoimmune diseases *(3)*. In addition, the recent development

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of digital ELISA (single molecular array, Simoa) allows an analytically sensitive measurement of type I IFN molecules in the sera of patients.

In children, the diagnosis of viral versus invasive bacterial infection is challenging since the main symptoms at onset are often similar and restricted to fever. Misdiagnosis is responsible for inappropriate antibiotic prescription, contributing to the emergence of multidrug resistant bacteria. Thus, we hypothesized that type I IFN, the key cytokine of antiviral response, may represent a new early biomarker of viral infection that could eventually help clinicians limit antibiotic overuse. The aim of this proof-of-concept study was to assess the performance of plasma IFN-α and IFN score in distinguishing documented viral and bacterial infections in a prospective cohort of children attending pediatric emergency departments for fever.

Materials and methods

PARTICIPANTS

This was an ancillary study of the prospective multicenter protocol ANTOINE (NCT03163628) (Fig. 1). Patients were included prospectively in this multicenter study from June 2017 to June 2019 (NCT03163628). The ANTOINE study was registered to the French National Data Protection Agency under the number 17-168 and was approved by an ethics committee for biomedical research in May 2017 (*Comité de Protection des Personnes Sud Méditerranée II*) under the number 217 R18. For each participant, written informed consent was obtained from parents or legal guardians for participation of the febrile children in the ANTOINE study. An additional specific written consent was needed to allow the participation of the present ancillary study. Inclusion and exclusion criteria are detailed in Table 1.

Febrile children aged from 7 days to 36 months attending a pediatric emergency department for a suspicion of infection were recruited prospectively in three different hospitals based in Lyon, Villefranche sur Saone, and Colombes in France. Inclusion criteria were fever for more than 6 h (temperature ≥38 °C between 7 days and 3 months and ≥38.5 °C between 3 months and 36 months) for which the physician prescribed venipuncture for suspected severe bacterial infection before any antibiotic treatment. For this study, Paxgene® tubes and serum were collected together with clinical blood tests.

Concomitantly, blood samples from 10 healthy volunteers were obtained from the national blood service (*Etablissement Français du Sang*, Lyon, France). We used the *Etablissement Français du Sang* standardized procedures for blood donation and followed provisions of articles R.1243–49 and the French public health code to obtain written non-opposition to the use of donated blood for research purposes from healthy volunteers. The blood donors' personal data were deidentified before transfer to our research laboratory. We obtained the favorable notice of the local ethics committee (*Comité de Protection des Personnes Sud-Est II*, Bâtiment Pinel, 59 Boulevard Pinel, 69 500 Bron) and acceptance from the French ministry of research (Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation, DC-2008-64) for the handling and conservation of these samples.

In addition, a pediatric disease control population (n = 9) with no infection nor characterized type I Interferonopathies was also selected among patients attending consultations at the National Referee Centre for Rheumatic and AutoImmune and Systemic diseases in childrEn (RAISE). This assessment was done on a routine basis in the referee center. This study was approved by the Hospices Civils de Lyon ethics committee under the number 2013-011B. The characteristics of pediatric control population are available in Supplemental Table 1.

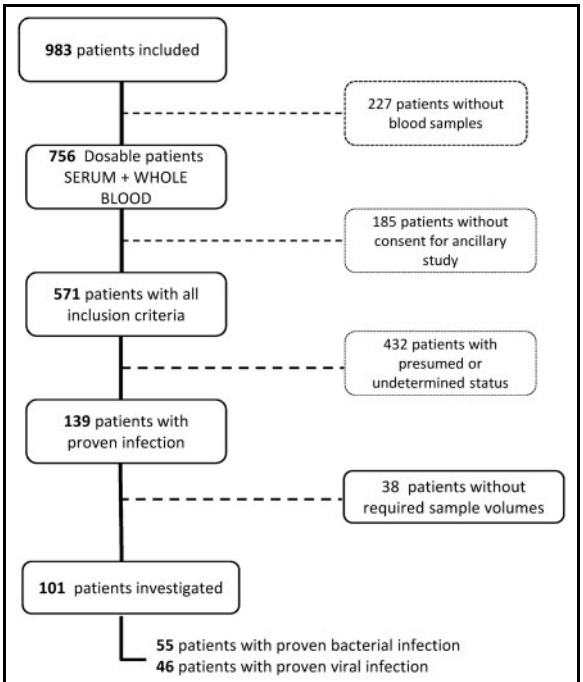

Fig. 1. Flow diagram of study population. Recruitment and flow of children presenting at the hospital with fever. An additional specific written consent was needed to allow the participation of the present ancillary study. The infections were proven on the basis of a definite identification of pathogens using routine microbiology testing. Assignment of patients to clinical groups was validated by consensus of an independent adjudication committee.

Table 1. Exclusion and inclusion criteria.

Inclusion criteria
Febrile children: • Between 7 days and 3 months old: fever >38 °C for more than 6 h (late neonatal fever suspected) for which the physician prescribed venipuncture • Between 3 months and 36 months old: fever ≥38,5 °C for more than 6 h and less than 7 days for which the physician prescribed venipuncture for suspected severe bacterial infection
Patient with national health insurance
Consent form signed by at least one parent/legal guardian
Exclusion criteria
Children treated by antibiotherapy within the past 48 h
Children with congenital or acquired immunodeficiency syndrome or long-term immunosuppression treatment
Children vaccinated within previous 48 h by an inactivated vaccine or within previous 10 days for the MMR (measles, mumps, and rubella) vaccines
Children with a chronic disease
Undergoing surgery within 7 days before inclusion

DIAGNOSTIC PROCESS

The ANTOINE study was designed to evaluate the performance of several biomarkers in "real-life" conditions. No other blood tests nor clinical investigation were performed beyond those requested by the emergency physician caring for febrile children. All patients underwent routine investigations as part of clinical care including blood count, C-reactive protein (CRP), blood chemistries, blood, stool and urine cultures, and cerebrospinal fluid analysis where indicated. Chest radiographs were undertaken as clinically indicated. Bacteria culture and viral diagnostics using multiplex PCR were performed by routine microbiological laboratories of each hospital. For patients with suspicion of respiratory tract infections, specific PCRs targeting influenza virus or respiratory syncytial virus were performed systematically during seasonal peak.

According to the routine microbiology results and the clinical parameters recorded in a numerical clinical record folder, we retained patients with proven viral (n = 46) or bacterial (n = 55) infections for this study (Table 2). The infections were proven on the basis of a definite identification of pathogens using routine microbiology testing. Assignment of patients to clinical groups was validated by consensus of an independent adjudication committee.

IFN-α AND IFN-γ ASSAY

Serum IFN-α concentrations (fg/mL) were determined by single molecule array (Simoa) using a commercial kit for IFN-α quantification (Quanterix™). The assay was based on a 3-step protocol using an HD- 1 Analyzer (Quanterix; *(4, 5)*). IFN-γ concentrations were measured using the simple plex kit IFN-γ assay with the Ella platform (Protein simple©), according to manufacturer's instructions.

IFN SCORE ASSESSMENT

RNA was extracted from whole blood contained in Paxgene® tubes (Kit PreAnalytix, Qiagen©) and quantified by spectrophotometric assay (Nanodrop 2000, Thermo Scientific™). RNA integrity was then evaluated by Agilent RNA microarray (Agilent Technologies©). mRNA quantification of 6 ISGs (*interferon alpha inducible protein 27 (IFI27), interferon induced protein 44 like (IFI44L), Interferon Induced Protein With Tetratricopeptide Repeats 1 (IFIT1), ISG15 Ubiquitin Like Modifier (ISG15), Radical S-Adenosyl Methionine Domain Containing 2 (RSAD2), Sialic Acid Binding Ig Like Lectin 1 (SIGLEC1)* and 3 housekeeping genes (*Actin Beta (ACTB), Hypoxanthine Phosphoribosyltransferase 1 (HPRT1), RNA Polymerase II Subunit A (POLR2A)*), was performed using nanostring technology (Nanostring Technologies©). Data standardization was obtained using the geometric mean of internal control and housekeeping genes count number. Interferon score was calculated as previously described *(6)*.

STATISTICAL ANALYSIS

Non-parametric Mann-Whitney tests and Spearman's correlation were calculated for all parameters using R software V3.6.1. A P-value <0.05 was considered statistically significant.

Results

Serum concentrations of IFN-α were below the quantification threshold (30 fg/mL) for 2% (1/46) of children with proven viral infections and for 71% (39/55) of children with bacterial infections ($P < 0.001$). Median [IQR] IFN-α concentrations were significantly higher in viral (7856 [3096–62 305] fg/mL) compared to bacterial infections (406 [68–3708] fg/mL, $P < 0.001$;

Table 2. Description of febrile patients.

Infection type	Bacterial		Viral		*P*-value
Population. n (%)	55 (54.5%)		46 (45.5%)		
Male. n (%)	20 (36.4%)[a]		27 (58.7%)[a]		<0.002[a]
Age, days, median [range]	396 [10–1094][b]		121 [10–903][b]		<0.002[b]
Duration of fever (h). n (%)[a]					<0.0001[a]
<12	4 (7.2%)		11 (23.9%)		
[12–24]	12 (21.8%)		15 (32.6%)		
>24	39 (70.9%)		20 (43.5%)		
C-reactive protein, µg/mL, median [range]	99.0 [0.24–571.2][b]		14.6 [0.6–198.0][b]		$<10^{-6}$[b]
Pathogens, n (%)	*Escherichia coli*	35 (63.6%)	Respiratory syncytial virus	13 (28.9%)	
	Streptococcus sp.	6 (10.1%)	Influenza virus	9[$] (19.6%)	
	S. pneumoniae	5 (9.1%)	[$] 1 co-infection influenza virus / norovirus		
	S. pyogenes	1 (1.8%)	Rotavirus	7 (15.6%)	
	Staphylococcus aureus	5 (9.1%)	*Picornavirus*	10 (21.7%)	
	Salmonella sp.	4 (7.3%)		7 Enterovirus (15.6%)	
	S. enteridis	2 (3.6%)		3 not specified (6.7%)	
	S. typhimurium	2 (3.6%)	Epstein-Barr virus	3 (6.7%)	
	Mycoplasma sp.	2 (3.6%)	Adenovirus	2 (4.4%)	
	M. pneumoniae	1 (1.8%)	Herpes simplex virus	1 (2.2%)	
	Fusobacterium necrophorum	1 (1.8%)	Measles morbillivirus	1 (2.2%)	
	Haemophilus influenzae	1 (1.8%)			
	Proteus mirabilis	1 (1.8%)			

[a]Chi^2 test revealed a statistically significant difference between the two groups.
[b]t-test revealed a statistically significant difference between the two groups.

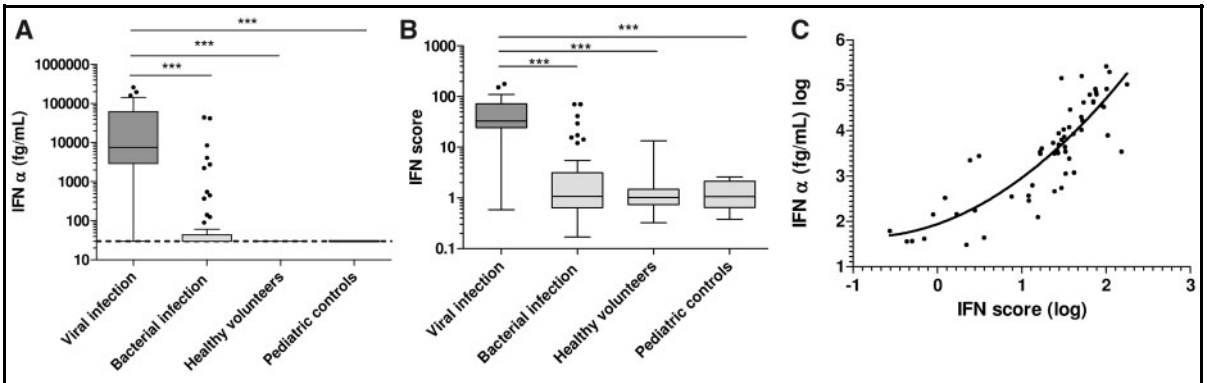

Fig. 2. Type I Interferon quantification in febrile children with proven viral or bacterial infection. A) IFN-α (fg/mL) measured by digital ELISA (SIMOA®). B) IFN score as defined by a 6 interferon stimulated gene transcriptional signature quantified using nanostring technology and obtained from Paxgene tubes from febrile infants with proven viral (n = 46) or bacterial (n = 55) infections attending pediatric emergency departments or from healthy controls (n = 10) or from pediatric controls (n = 9). Limit of quantification is indicated by the dotted lines. The IFN-α kit (Quanterix™) used for this study detect IFN-α type 2. C) Spearman correlation between IFN score and serum IFN-α concentrations. For Fig. 2A and 2B, the box-and-whisker plots represent the median and inter-quartile range; whiskers were calculated by the Tukey's method. Mann-Whitney U test ***$P<0.001$. IFN (Interferon).

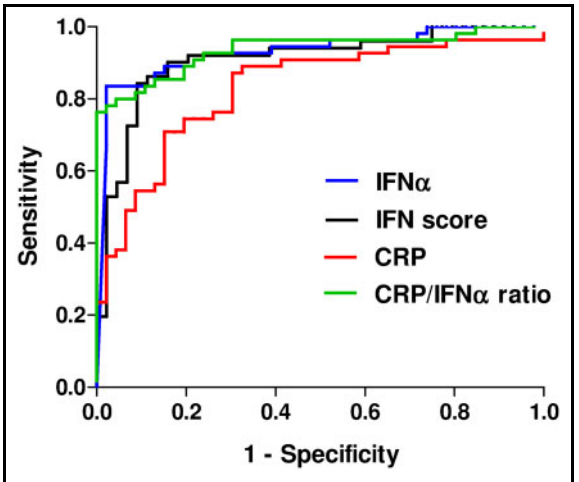

Fig. 3. Receiver operating characteristic curve of C-reactive protein (CRP), IFN score, serum IFN-α, and CRP/IFN-α ratio concentrations to discriminate between viral and bacterial infections. Analysis performed from data shown in Fig. 2. Mann-Whitney U test ***$P<0.001$ – IFN (interferon); CRP (C-reactive protein).

Fig. 2A). Similarly, the IFN score was increased 30-fold in viral infections compared to bacterial ones ($P < 0.001$; Fig. 2B). Interestingly, no significant difference was observed between febrile children with bacterial infections and healthy volunteers or control pediatric population. There was a strong positive correlation between serum IFN-α concentrations and the IFN score (r-spearman [95%CI] 0.85 [0.76; 0.91], Fig. 2C).

Analysis of the area under the curve [95%CI] showed that both IFN-α serum concentration (0.930 [0.877; 0.983]) and IFN score (0.908 [0.845; 0.971]) robustly discriminated viral infections from bacterial ones in febrile children (Fig. 3). To evaluate if IFN-α could improve the diagnosis of febrile children attending pediatric emergency departments, we assessed the performance of this biomarker in combination with a clinically validated test that is CRP quantification. The area under the curve shown in Fig. 3 revealed that the ratio of the concentrations of CRP and IFN-α strongly improves the classification of these patients compared to CRP alone (0.936 [0.888; 0.985] versus 0.829 [0.747; 0.910] respectively, Fig. 3).

In addition, knowing that ISG expression may also be driven by Type II interferon, we then evaluated whether serum IFN-γ concentrations would correlate with the IFN score. No significant difference was observed between IFN-γ serum concentrations for children with viral infections compared to those with bacterial infections (Fig. 4A). Additionally, there was no relation between ISG expression and Type II interferon circulating concentrations (r-spearman 0.18 [-0.054; 0.407]; Fig. 4B).

Discussion

Biomarkers have become key tools during the clinical decision-making process for clinicians dealing with

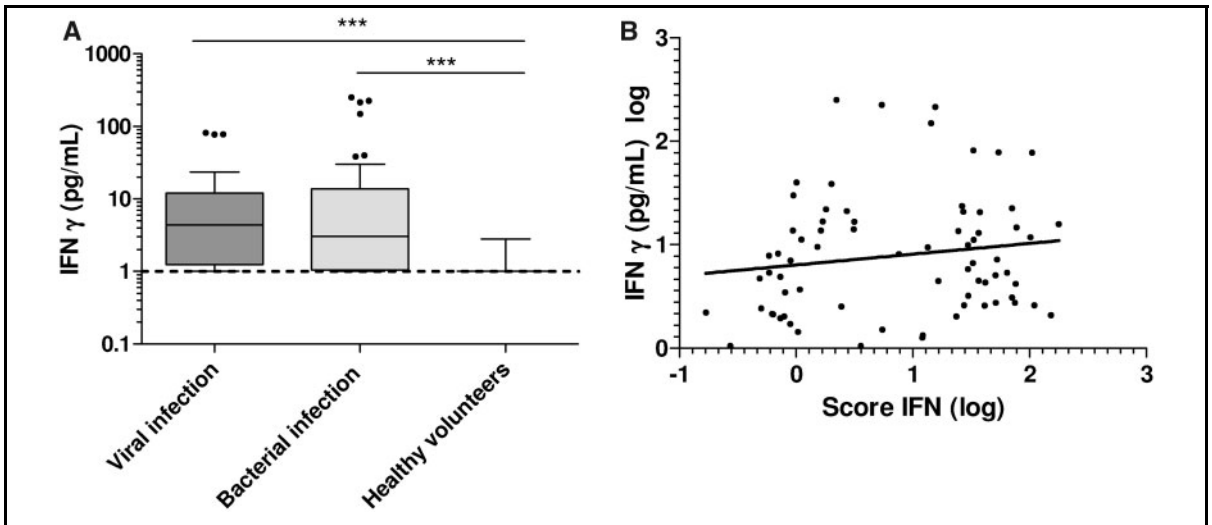

Fig. 4. Type II Interferon quantification in febrile children with proven viral or bacterial infection. A) IFN-γ (pg/mL) measured in serum from febrile infants with proven viral (n = 46) or bacterial (n = 54) infections attending pediatric emergency departments One patient with bacterial infection had insufficient blood volume and IFN-γ measurement was not performed. Box-and-whisker plots represent the median and inter-quartile range, whiskers calculated by the Tukey's method. Mann-Whitney U test ***P<0.001. B) Spearman correlation between IFN score and serum IFN-γ concentrations.

febrile children. In the pediatric emergency department, CRP, procalcitonin (PCT), and white blood cell count are probably the most used markers despite their poor clinical performance in guiding antibiotic prescription in such clinical settings *(7)*. In combination with a biomarker specific for bacterial infections, a specific biomarker for viral infections could improve the management of febrile children. Recent clinical studies have shown that the combination of CRP or PCT with myxovirus resistance protein 1, coded by the ISG *mx1*, strongly improved both the clinical sensitivity and specificity for differentiating infectious etiology *(8, 9)*. Nevertheless, myxovirus resistance protein 1 is an intracellular protein that prevents the quantification of this protein in serum or plasma, the method currently used for dosage of CRP or PCT in routine laboratories *(10)*. Here, we assessed by digital ELISA the performance provided by the measurement of protein IFN-α itself, which is secreted by immune cells after recognition of viruses and detectable in serum or plasma. This preliminary study showed that IFN-α, at the protein level, is increased in blood of febrile infants with viral infections.

Moreover, the biomarkers performance reported in this study have been evaluated in the ANTOINE clinical trial performed in "real-life" conditions. In our cohort, only 15% of patients had a definite infection based on the routine microbiology results and the clinical parameters, in line with previous reports showing that laboratory tests failed to identify a causative pathogen in over half of children with severe illness or fever, leaving an important place for biomarkers to improve the management of febrile children *(11, 12)*. In our study, the microbiological investigation was not exhaustive for each patient, explaining probably the low prevalence of rhinoviruses in our cohort. Consequently, viral co-infection was not investigated/reported in our cohort. This could explain the high concentration of interferon alpha observed for some patients with a documented bacterial infection.

The alternative to IFN-α protein quantification, represented by an IFN score measurement, was also evaluated in this study. The results showed that this ISG-based signature had the same diagnostic performance than IFN-α protein quantification. Fast track RNA analyses using Nanostring® or FilmArray® platforms could thus be helpful in implementing this biomarker in routine use. Of note, in cases of viral infections, the circulating IFN-α concentrations, as well as the IFN scores reported herein, were of the same order of magnitude as those observed in cases of autoimmune disease such as systemic lupus erythematosus *(13)*. Moreover, several recent studies suggest that IFN-α could be a useful biomarker to monitor interferonopathy disease activity, to identify patients with high risk of relapse, and to select the best candidates for anti-IFNα treatment *(5, 14, 15)*. Our results suggest that viral infections could interfere and possibly be responsible

for false positive diagnoses when the IFN score or IFN-α protein is used for the screening and the monitoring of autoimmune diseases.

Of note, recent published data demonstrated that, in specific clinical diseases such as *Mycobacterium tuberculosis* infections, interferon-stimulating genes (ISG) expression was not mediated through plasma type I IFN *(16)*. However, in febrile infants, our results showed that the expression of ISG was driven by IFN-α and not by IFN-γ.

According to the 68th World Health Assembly declaration, it is urgent to find effective diagnostic tools to guide optimal antibiotic use *(17)*. Our study showed that measurement of IFN-α femtomolar concentrations, as well as the use of an IFN score, could offer new perspectives for improving diagnosis and limiting antibiotic overuse in febrile infants. The performance of IFN-α needs to be confirmed in a larger cohort of febrile children with suspected and proven infections.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Disclosures: Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

S. Trouillet-Assant, Y. Gillet and E. Javouhey conceived the study, planned, designed and interpreted experiments and wrote the initial draft. Biobanking of samples and cytokines quantification experiments were undertaken by S. Pons and L. Boisselier. A. Ouziel and K. Brengel-Pesce interpreted the microbiological data and critically reviewed the manuscript. P. Rebaud, R. Basmaci, N. Droz and A. Belot provided clinical samples and critically reviewed patient data. S. Viel performed transcirptomic analysis and generated figures. Antoine Study group members significantly contributed to clinical, biological and microbiological data and patient's follow. All authors reviewed the manuscript and agreed to its submission.

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References

1. Psarras A, Emery P, Vital EM. Type I interferon-mediated autoimmune diseases: pathogenesis, diagnosis and targeted therapy. Rheumatology (Oxford) 2017;56:1662–75.
2. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nat Rev Immunol 2015;15:87–103.
3. Rice GI, Melki I, Frémond M-L, Briggs TA, Rodero MP, Kitabayashi N, et al. Assessment of type I interferon signaling in pediatric inflammatory disease. J Clin Immunol 2017;37:123–32.
4. Rissin DM, Kan CW, Campbell TG, Howes SC, Fournier DR, Song L, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat Biotechnol 2010;28:595–9.
5. Mathian A, Mouries-Martin S, Dorgham K, Devilliers H, Barnabei L, Ben Salah E, et al. Monitoring disease activity in systemic lupus erythematosus with single-molecule array digital enzyme-linked immunosorbent assay quantification of serum interferon-α. Arthritis Rheumatol. 2019;71:756–65.
6. Pescarmona R, Belot A, Villard M, Besson L, Lopez J, Mosnier I, et al. Comparison of RT-qPCR and Nanostring in the measurement of blood interferon response for the diagnosis of type I interferonopathies. Cytokine 2019; 113:446–52.
7. van der Does Y, Limper M, Jie KE, Schuit SCE, Jansen H, Pernot N, et al. Procalcitonin-guided antibiotic therapy in patients with fever in a general emergency department population: a multicentre non-inferiority randomized clinical trial (HiTEMP study). Clin Microbiol Infect 2018;24:1282–9.
8. Self WH, Rosen J, Sharp SC, Filbin MR, Hou PC, Parekh AD, et al. Diagnostic accuracy of FebriDx: a rapid test to detect immune responses to viral and bacterial upper respiratory infections. J Clin Med 2017;6. pii: E94.
9. Shirley M. FebriDx®: a rapid diagnostic test for differentiating bacterial and viral aetiologies in acute respiratory infections. Mol Diagn Ther 2019;23:803–9.
10. Zav'yalov VP, Hämäläinen-Laanaya H, Korpela TK, Wahlroos T. Interferon-inducible myxovirus resistance proteins: potential biomarkers for differentiating viral from bacterial infections. Clin Chem 2019;65: 739–50.
11. Bleeker-Rovers CP, Vos FJ, de Kleijn EMHA, Mudde AH, Dofferhoff TSM, Richter C, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore) 2007; 86:26–38.
12. Martinón-Torres F, Salas A, Rivero-Calle I, Cebey-López M, Pardo-Seco J, Herberg JA, et al. Life-threatening infections in children in Europe (the EUCLIDS project): a prospective cohort study. Lancet Child Adolesc Health 2018;2:404–14.
13. Oke V, Gunnarsson I, Dorschner J, Eketjäll S, Zickert A, Niewold TB, et al. High levels of circulating interferons type I, type II and type III associate with distinct clinical features of active systemic lupus erythematosus. Arthritis Res Ther 2019;21:107.
14. Mathian A, Mouries-Martin S, Dorgham K, Devilliers H, Yssel H, Garrido Castillo L, et al. Ultrasensitive serum interferon-α quantification during SLE remission identifies patients at risk for relapse. Ann Rheum Dis 2019;78: 1669–76.
15. Melki I, Devilliers H, Gitiaux C, Bondet V, Duffy D, Charuel J-L, et al. Anti-MDA5 juvenile idiopathic inflammatory myopathy: a specific subgroup defined by differentially enhanced interferon-α signalling. Rheumatology (Oxford) 2019.
16. Llibre A, Bilek N, Bondet V, Darboe F, Mbandi SK, Penn-Nicholson A, et al. Plasma type I IFN protein concentrations in human tuberculosis. Front Cell Infect Microbiol 2019;9:296.
17. WHO. Antimicrobial resistance: global report on surveillance. WHO Library Cataloguing-in-Publication Data; 2014. https://www.who.int/antimicrobial-resistance/publications/surveillancereport/en/.