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Evaluation of post-infectious inflammatory reactions in a retrospective study of 3 common invasive bacterial infections in pediatrics

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Abstract

Infectious diseases can result in unanticipated post-infectious inflammatory reactions (PIIR). Our aim was to explore PIIR in 3 frequent pediatric bacterial invasive infections in France by a retrospective monocentric study. We included children hospitalized between 2003 and 2012 for *Streptococcus pneumoniae* (SP), *Neisseria meningitidis* (NM), or *Streptococcus pyogenes* invasive infections. The PIIR had to have occurred between 3 and 15 days without fever despite an individually tailored antibiotic therapy. A descriptive analysis was carried out to determine PIIR risk factors. We included 189 patients, of whom 72, 79, and 38 exhibited invasive infections caused by *S pyogenes*, SP, and NM, respectively. The mean age was 44 months. PIIR were observed in 39 cases, occurring after a median of 8 days (5–12), with a median duration of 3 days (2–6). Fever, arthritis, and pleural effusion were observed in 87%, 28.2%, and 25.6%, respectively. In multivariate analysis, PIIR were associated with pleuropneumonia, hospitalization in an intensive care unit (ICU), and elevated C-reactive protein (CRP). PIIR were observed in 20% of children after SP, NM, or *S pyogenes* invasives infections. Their occurrence was associated with the initial severity but not the etiological microorganism. Further studies are warranted to confirm these findings.

Abbreviations: CAP = community-acquired pneumonia, CI = confidence interval, CNSI = central nervous system infection, CRP = C-reactive protein, ENT = ears, nose, and throat, GAS = group A Streptococcus, GASII = group A *Streptococcal* invasives infection, ICU = intensive care unit, NM = *Neisseria meningitides*, NMII = *Neisseria meningitidis* invasive infection, NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, PIIR = post-infectious inflammatory reactions, SP = *Streptococcus pneumonia*, SPII = *Streptococcus pneumoniae* invasive infection.

Keywords: innate immunity, invasive bacterial infection, *Neisseria meningitidis*, pediatrics, post-infectious inflammatory, *Streptococcus pneumonia*, *Streptococcus pyogenes*

1. Introduction

Inflammation is one of the main physiological responses against infectious diseases that can result in "collateral damage." Even when the infectious agent has been eliminated, the inflammatory response can be delayed and result in post-infection inflammatory reaction (PIIR). PIIR comprise a broad spectrum of manifestations according to the etiologic agent. For example, Multisystem Inflammatory Syndrome in Children associated with COronaVIrus Diseases 2019 infection was recently described,[1] or post- infectious reactions that have been reported for group A *Streptococcus* (GAS) infections. GAS PIIR comprise acute rheumatic fever, acute post-streptococcal glomerulonephritis, autoimmune neuropsychiatric disorders associated with streptococcal infections, and reactive arthritis. Rheumatic fever is a model of PIIR, the factors involved can include the specific genotypes of GAS, an abnormal immune response, a molecular mimicry

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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mechanism, genetic susceptibility of the host, and repeated GAS infections.[2,3]

PIIR are usually attributed to established autoimmune mechanisms that are due to specific autoantibodies, such as acquired S protein deficiency following Varicella-Zoster Virus, and Human Herpes Virus-6 infection, with a putative breaking tolerance due to molecular mimicry between viral antigen and S protein.[4,5] Beyond these examples there are no robust data that confirm involvement of autoimmunity in most of PIIR.

As PIIR can be quite diverse, in order to investigate PIIR without being restricted by preconceived notions regarding the involvement of acquired immunity and irrespective of the causative agents, we decided to focus on 3 bacterial invasive childhood infections that are common in France, namely *Streptococcus pneumoniae* (SP), *Neisseria meningitidis* (NM), and group A *Streptococcus* invasive infections (GASII).

The main objective of our study was to determine the frequency and the characteristics of PIIR following pneumococcal invasive infections (Streptococcus pneumoniae invasive infection [SPII]), Neisseria meningitidis invasive infection (NMII), or GASII. We also determined the predictors of PIIR, with the aim of identifying warning symptoms as well as signs that are associated with immunological pathways, such as elevated C-reactive protein (CRP) levels with autoinflammatory diseases.

2. Methodology

In order to characterize PIIR after SPII, NMII, and GASII, and to identify risk factors, we undertook a retrospective longitudinal study between the 1st of January 2003 and the 31st of December 2012 of patients <18 years of age who had been hospitalized at the University Hospital of Montpellier. After December 2012, medical software was introduced in our institution that, unfortunately, was not suitable for checking temperature curves. Consequently, in order to avoid an inclusion bias, we ended eligibility for this study at the time that this new software was implemented.

The inclusion criteria comprised being <18 years of age and having a fever associated with a SP, NM, or GASII. Invasive infections were defined as the identification of an infectious agent in sterile tissue. We used the bacterial database to identify all of the positive samples for GAS, SP, or NM. Data were collected from individual medical records that are standardized in our hospital, electronic records for pathology, and radiology results, as well as electronic inpatient medication prescriptions and discharge prescriptions, and these were converted into digital records using Excel® software.

In each case associated with the identification of the causative agent, we defined several disorders, with their diagnostic criteria, based on the final diagnosis and controlled by an independent physician (Supplemental data 1, Supplemental Digital Content 1, http://links.lww.com/MD/H272): community-acquired pneumonia (CAP); pleuropneumonia; septic arthritis; central nervous system infection (CNSI) including meningitis and meningoencephalitis; ears, nose, and throat (ENT) infections; and peritonitis. In order to evaluate hemodynamic tolerance, we defined "signs of sepsis" as the presence of decreased capillary filling or mottling, tachycardia, low systolic blood pressure, and oliguria.

The exclusion criteria were: incomplete medical records; children transferred to another center during the treatment (to avoid the risk of using inaccurate information); patients who refused to allow their data to be used for this study; diagnosis of a hereditary or acquired immune deficiency, cystic fibrosis, or active secondary infections; and children who had succumbed to their infection.

Active infections were defined by the identification of an active infectious agent that could explain the symptoms, or an active infectious process confirmed by a physician.

PIIR were defined as the presence of clinical inflammatory manifestations occurring between 3 and 15 days after the end of the initial infectious episode, defined by apyrexia for at least 3 consecutive days and improvement of the primary disease under individually tailored antibiotic therapy. These clinical inflammatory manifestations included: rebound of fever (temperature >38°C), arthritis, reactional pleural effusion, intra-abdominal effusion, orchitis or epididymitis, and cutaneous manifestation (rash, erythema nodosum, cheilitis). The skin rashes could be nodules with erythema nodules, petechia, bubble eruptions, or scarlatiniform eruptions. We excluded the recurrence of infection based on negative samples on microbiology assays, without the presence of an infectious process such as an abscess.

PIIR were subdivided into 2 categories: confirmed PIIR for patients with clinical improvement in the absence of modification or re-administration of the antibiotic therapy; and probable PIIR in cases of clinical improvement with a modification or re-administration of the antibiotic therapy.

The study was approved by the Research Ethics Committee of our institution under reference NCT04594785 and an application for authorization of the processing of personal data was obtained from the National Commission on Informatics and Liberty.

In order to determine the risk factors, the population was divided into 2 groups based on the presence or absence of PIIR, that is, a PIIR group (PIIR+) and a no-PIIR group (PIIR-).

2.1. Statistical analyses

A descriptive analysis of the general population and of each group was carried out with the qualitative data expressed as percentages, and the quantitative data expressed as means ± the standard deviation or as medians with the Q25 and Q75 quartiles. Logistic regression models were applied in order to determine factors associated with PIIR. The variables with P values of <.15 were then retained for multivariate logistic regression. A P value <.05 in the multivariate model after a stepwise selection of variables was considered significant. Some of PIIR were subjected to a specific subgroup analysis in order to avoid cases of active infections.

The statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

3. Results

During the study period, 263 children met the inclusion criteria for invasive infection. Seventy-four patients met the exclusion criteria. Twenty-seven (10%) of them were excluded due to a lack of data, eleven (4%) as a result of probable or proven active secondary infections. Thus, 189 patients were selected, 72 with GASII, 79 with SPII, and 38 with NMII (Fig. 1).

3.1. Population characteristics

The population characteristics are summarized in Table 1. The mean age was 43.96 months (± 45.46), and the sex ratio was 1.39 (109 males and 80 females). The proportion of patients according to the season (autumn, winter, spring, and summer) was 32.3%, 35.5%, 18.5%, and 13.8%, respectively. There were 38 NMII, 72 GASII, and 79 SPII. The most common invasive infections were CNSI, ENT infections, CAP, pleuropneumonia, and septic arthritis, with 56, 56, 23, 15, and 14 patients, respectively.

During the primary episode, the average duration of the fever was 5 days, and the maximum temperature was 39.6°C. The median time between the onset of fever and the start of antibiotic treatment was 2 days. Corticosteroid therapy was administered to 51 patients (27%).

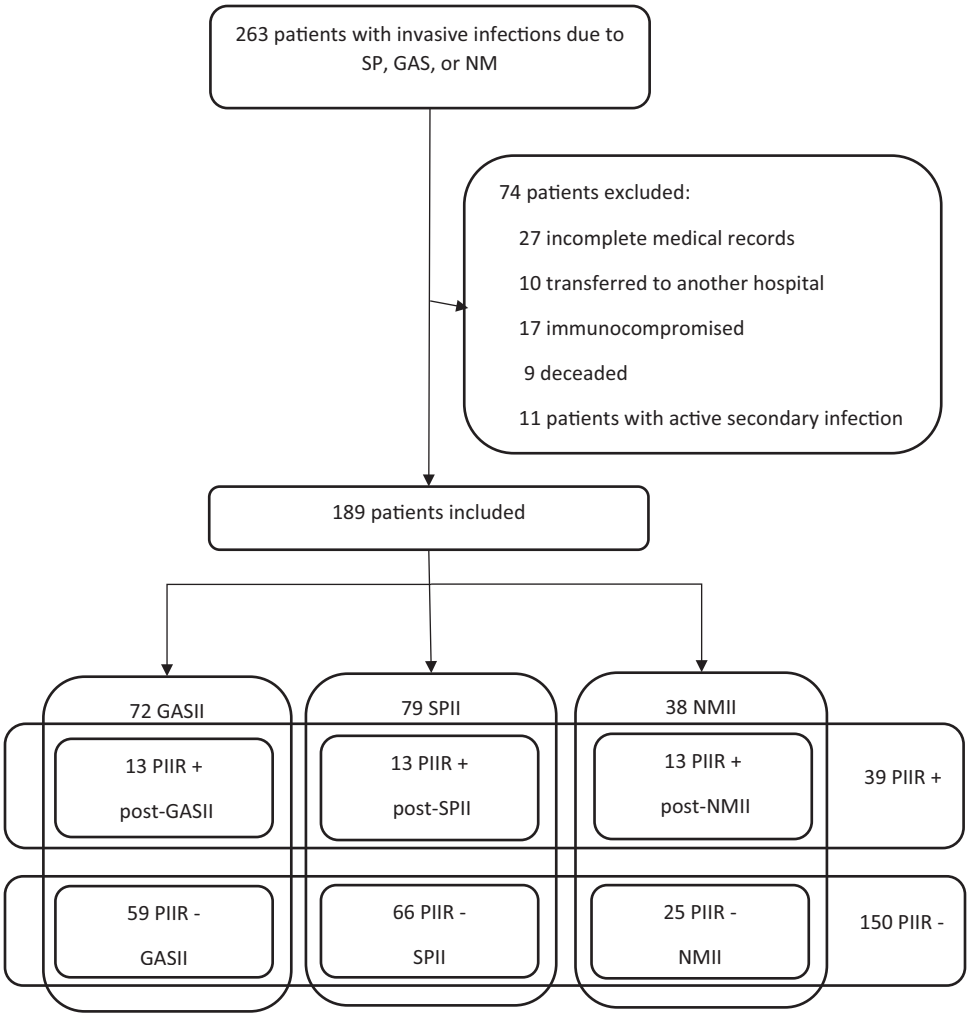

Figure 1. Flowchart of inclusions. GAS = group A *Streptococcus*, GASII = group A *Streptococcus* invasive infection, NM = *Neisseria meningitides*, NMII = *Neisseria meningitides* invasive infection, PIIR = post-infectious inflammatory reactions, SP = *Streptococcus pneumonia*, SPII = *Streptococcus pneumonia* invasive infection.

3.2. Occurrence of PIIR

Overall, 39/189 patients (20.6%) developed PIIR after the initial infectious episode. The characteristics of the children with PIIR are presented in Table 1. PIIR episodes were more frequent in winter (46%), while PIIR- cases were more frequent in autumn (36%), although this difference was not significant.

The most frequent primary diseases in the PIIR+ group were CNSI, with 17 cases (43.6%); pleuropneumonia, with 13 cases (33.3%); and arthritis, with 5 cases (12.8%). For the PIIR- group, the distribution was 56 ENT infections (37.3%), 39 CNSI (26%), and 22 cases of CAP (14.7%) (Table 1). Analysis of the etiological agent indicated that PIIR occurred in 34% of the NMII, 16% of the SPII, and 18% of the GASII.

3.3. PIIR characteristics

The PIIR characteristics are summarized in Table 2. The PIIR occurred after a mean of 3.8 days after the end of the initial infectious episode and had a mean duration of 4.7 (±3.8) days. All resolved without any sequelae. Sixteen (41%) of the patients with a PIIR exhibited at least 2 distinct inflammatory manifestations. Fever, which was observed in 34 cases (87%), was the most common PIIR. Eleven patients (28.2%) exhibited arthritis, which was polyarticular for 3 patients, and the most affected joint was the knee. Other manifestations were pleural effusion in 10 patients (25.6%), orchitis or epididymitis in 4 patients (10.3%), dermatological manifestations (scarlet rash or erythema nodosum) occurred in 2 children, and intra-abdominal effusion in one patient. Two patients (5.13%) exhibited sepsis sign(s) during the PIIR.

The levels of inflammatory markers were recorded for 34 patients (87%) during the PIIR. The median maximum CRP level was 60.5 mg/L (interquartile range: 18.9–129.5). Most of the patients (76.9%) had bacteriological and/or virological sampling during their PIIR that were negative: a blood culture in 22 cases, a urine culture in 7 cases, a lumbar puncture in 6 cases, synovial fluid in 6 cases, a pleural puncture in 5 cases, viral analysis, sputum culture in 3 cases, and peripheral or central catheter sampling in 3 cases. The antibiotic therapy was changed for 14 patients (35.9%). Corticosteroids were administered to 10 patients (25.6%), with an average duration of 17 days. The average PIIR duration was 6 days in the group treated with corticosteroid and 4 days for the patients who did not receive corticosteroids.

3.4. Analysis of the risk factors for PIIR

In univariate analysis, the type of bacteria, the level of the initial fever, the presence of sepsis signs, elevated CRP and procalcitonin levels, infectious pleural effusion, CNSI, hospitalization in

Table 1

Description of the population: manifestation of the initial infectious episode.

		PIIR + group (N = 39)	PIIR- group (N = 150)	All children (N = 189)	*P*
Mean age (yr)		41.0 ± 33.3	44.7 ± 48.2	43.9 ± 45.5	.634
Males		26 (66.7%)	83 (55.3%)	109 (57.7%)	
Maximum temperature (°C)		**39.8 ± 0.7**	**39.5 ± 0.7**	**39.6** ± 0.72	**.018**
Duration of fever (d)		5 ± 3.4	4.9 ± 3.4	4.9 ± 3.4	.749
Maximum CRP (mg/L)		**254.9 ± 112.4**	**146.4 ± 98.6**	**168.9**	**<.001**
Maximum PCT (ng/mL)		**60.7 ± 81.4**	**13.4 ± 37.1**	**24.3**	**<.001**
Sign(s) of sepsis		**16 (41%)**	**23 (15.3%)**	**39 (20.6%)**	**.004**
ICU stay		**23 (59%)**	**21 (14%)**	**34**	**<.001**
Use of steroids		**17 (43.6%)**	**34 (22.7%)**	**51 (27%)**	**.009**
Initial diagnosis	CNSI	17 (43.6%)	39 (28.1%)	56 (31.5%)	**<.001**
	Pleuropneumonia	13 (33.3%)	2 (1.4%)	15 (8.4%)	
	Arthritis	5 (12.8%)	9 (6.5%)	14 (7.9%)	
	Peritonitis	2 (5.1%)	1 (0.7%)	3 (1.7%)	
	ENTI	0	56 (40.3%)	56 (31.5%)	
	CAP	1 (2.6%)	22 (15.8%)	23 (12.9%)	
	Other	1 (2.6%)	10 (7.2%)	11 (6.2%)	
Season	Autumn	7 (18%)	54 (36%)	61 (32.28%)	.178
	Winter	18 (46.2%)	49 (32.7%)	67 (35.45%)	
	Spring	8 (20.5%)	27 (18%)	35 (18.52%)	
	Summer	6 (15.4%)	20 (13.3%)	26 (13.76%)	
Microorganisms	NM	13 (33.3%)	25 (16.7%)	38 (20.1%)	.066
	SP	13 (33.3%)	66 (44%)	79 (41.8%)	
	GAS	13 (33.3%)	59 (39.3%)	72 (38.1%)	

CAP = community-acquired pneumonia, CNSI = central nervous system infection, CRP = C reactive protein, ENTI = ear, nose, and throat infection, GAS = group A *Streptococcus*, ICU = intensive care unit, NM = *Neisseria meningitidis*, PCT = procalcitonin, PIIR = post-infectious inflammatory reactions, SP = *Streptococcus pneumoniae*.

Table 2

Characteristics of the PIIR + group.

	N	Mean (± standard deviation)	Median (Q25–Q75)
Between infection and PIIR			
Time between onset and PIIR (d)	39	8.6 (±4.91)	8 (5–12)
Time between primary apyrexia and PIIR (d)	38	3.8 (±2.32)	3 (2–5)
Time between steroids termination and PIIR (d)	16	2.4 (±3.18)	2.5 (2–4)
During PIIR			
PIIR maximum temperature (°C)	35	39.0 (±0.62)	38.7 (38.5–39.5)
Maximum CRP during PIIR (mg/L)	34	79.3 (±66.78)	60.5 (18.9–129.5)
Maximum PCT during PIIR (ng/mL)	21	5.4 (±10.13)	1.1 (0.5–3.3)
PIIR duration (d)	39	4.5 (±3.75)	3 (2–6)
Number of PIIR manifestations	39	1.6 (±0.91)	1 (1–5)
Duration of steroid therapy during PIIR (d)	10	17.3 (±16.02)	11 (7–23)
Duration between start of steroids and end of PIIR (d)	10	2.2 (±3.52)	1 (1–2)

CRP = C reactive protein, PCT = procalcitonin, PIIR = post-infectious inflammatory reactions.

an intensive care unit (ICU), and use of corticosteroids in the initial management of the infectious episode were associated with PIIR. Multivariate analysis showed that only pleuropneumonia, hospitalization in an ICU, and elevated CRP levels in the initial assessment were risk factors for PIIR (Table 3).

As a sensitivity analysis, we restricted the model to children with confirmed PIIR (16 cases) (Table S1, Supplemental Digital Content 2, http://links.lww.com/MD/H273). The same factors remained strongly associated with PIIR. Multivariate analysis showed significant results for ICU hospitalization, pleuropneumonia, and CNSI, with ORs of 14.6 (95% confidence interval [CI]: 2.62–81.85), 80.63 (4.22 to >999.99), and 7.62 (0.81–72.07), respectively.

As severe infections can be treated with corticosteroids, which are known to promote fever rebound,[6] We carried out the analysis after exclusion of the patients who had been administered steroids for their initial episode. Thus, the analysis was carried with 22 PIIR+ and 116 PIIR- patients. In univariate analysis, we found an association with hospitalization in the ICU, the presence of signs of sepsis-like features, NMII, diagnosis of septic arthritis, and elevated CRP levels, with Ors of 12.75, 4.66, 3.95, 3.95, and 1.46, respectively (Table S2, Supplemental Digital Content 3, http://links.lww.com/MD/H274). In multivariate analysis, only hospitalization in an ICU was associated with PIIR, with an odds ratio (OR) of 64 (95% CI: 6.95–592.43; $P = .0002$). Due to this strong association with hospitalization in an ICU in multivariate analysis, we excluded this information from the final analysis (Table S3, Supplemental Digital Content 4, http://links.lww.com/MD/H275). We found an association with elevated max CRP, with an OR of 1.57 (95% CI: 1.10–2.25; $P = .013$) and a protective effect of a short period between the onset of the disease and the start of antibiotic therapy, with an OR of 0.54 (95% CI: 0.03–0.96; $P = .035$). Yet corticosteroids are also provided to manage PIIR. They were prescribed in 26% of the PIIR cases and they were maintained for an average duration of 17 days.

4. Discussion

To the best of our knowledge, this is the first study to systematically explore PIIR events for 3 different bacterial invasive infections. We found that PIIR occurred in approximately 20% of GASII, NMII, and SPII PIIR in the first 15 days following the onset of the infection., irrespective of the 5 patients excluded due to a confirmed infectious etiology.

If we focus on meningitis, we have founded 17/56 (30%) PIIR, in a Dutch study that included 130 children hospitalized for an invasive meningococcal infection, 15.3% of the children exhibited inflammatory manifestations. The authors did not consider isolated fever as an inflammatory reaction. These manifestations were oligo- and polyarthritis in 13.8% of the cases, vasculitis in 8.4% of the cases, and pleural effusion in 3.8% of the cases. Sixty percent of these

Table 3

Risk factors of PIIR + group in univariate and multivariate analysis.

	Univariate analysis				Multivariate analysis			
	Odds ratio	95% CI		*P* value	Odds ratio	95% CI		*P* value
NMII vs SPII	2.64	1.08	6.47	.03				
GASII vs SPII	1.12	0.48	2.60	.79				
Sign(s) of sepsis	**3.84**	**1.77**	**8.36**	**<.01**				
Steroids at the onset of disease	**2.64**	**1.26**	**5.52**	**.01**				
Autumn vs spring	0.44	0.14	1.33	.15				
Winter vs spring	1.24	0.48	3.23	.66				
Summer vs spring	1.01	0.30	3.38	.98				
Age (mo)	1	0.99	1.01	.65				
Maximum temperature (°C)	**1.79**	**1.07**	**2.98**	**.03**				
Maximum CRP level (mg/L)*	**1.61**	**1.33**	**1.94**	**<.01**	**1.49**	**1.06**	**2.11**	**.02**
Maximum PCT level (ng/L)	**1.02**	**1.01**	**1.03**	**<.01**				
Time before initiation of Antibiotics	0.92	0.79	1.07	.26				
Duration of the fever	1.01	0.91	1.12	.85				
Hospitalization in an ICU	**8.83**	**4.02**	**19.40**	**<.01**	**18.2**	**5.31**	**62.32**	**<.01**
Diagnosis of CAP	**0.15**	**0.02**	**1.17**	**.07**				
Diagnosis of pleuropneumonia	**36.98**	**7.88**	**173.48**	**<.01**	**23.88**	**3.58**	**62.32**	**<.01**
Diagnosis of septic arthritis	2.30	0.73	7.32	.16				
CNSI	**2.20**	**1.06**	**4.57**	**.03**				
ENTI	–	–	–	NA†				

CAP = community-acquired pneumonia, CI = confidence interval, CNSI = central nervous system infection, CRP = C reactive protein, ENTI = ears, nose, and throat infection, GASII = group A *Streptococcus* invasive infection, ICU = intensive care unit, NMII = *Neisseria meningitidis* invasive infection, PCT = procalcitonin, PIIR = post-infectious inflammatory reactions, SPII = *Streptococcus pneumoniae* invasive infection.

*The indicated odds-ratio for CRP corresponds to a 50 mg/L increase in the CRP level.

†As none of the patients in the PIIR+ group had an ENTI, the odds-ratio could not be calculated.

children exhibited at least 2 inflammatory manifestations.[7] In another multicenter study involving 476 hospitalized children that included bacterial meningitis irrespective of the causative agent, secondary fever occurred in 16% of the included children. In 39% of the cases, no explanation for this fever was found, and in 27% of the cases, it was related to a nosocomial infection (4% of the total population), while in our series there were no bacterial nosocomial infections..[8] One monocentric retrospective study have assessed secondary fever in bacterial meningitis without limitation regarding etiologic agent, One retrospective study aim to described clinical features of secondary fever in 52 bacterial meningitis, they observed 57% of recurrent fever.[9] A Cochrane database meta-analysis regarding corticosteroid therapy in acute bacterial meningitis, has evaluated 12 studies mixing adults and children that has included 1723 patient, recurrent fever were observed in 25% of cases, these episodes occurred more often in corticosteroid-treated participants (relative risk 1.27, 95% CI 1.09–1.47).[10]A recent meta-analysis, focalized on corticosteroid therapy in pediatric acute meningitis has evaluated 9 studies that have included 1159 patients and have reported 34% of secondary fever that were more frequent in corticosteroid-treated participants (relative risk 1.23, 95% CI–1.51)[11] Thus in bacterial meningitis, secondary fever episodes that could be consider as a PIIR are observed in 15% to 57% of PIIR. This range of results could be explain by the heterogeneity of studies, but inconsistent with our data. For GASII, we have already described 2 cases of this type of PIIR.[12]

For pleural effusion we do not have found equivalent studies. For arthritis evaluated on study that have included 71 septic arthritis have observed in 8.5%, relapse of arthritis, that were all aseptic and associated with an inflammatory syndrome, these episodes were and compatible with our PIIR definition,[13]

Clinical risk factors have been studied in meningococcal diseases, a study analyzing 2 clinico-biological scores of severity, the Pediatric risk of mortality score and the glasgow meningococcal septicemia prognostic score, found no correlation between these scores and the occurrence of an inflammatory manifestation.[7] An earlier study found a higher risk of developing an inflammatory manifestation in case of clinical signs of septic shock or the presence of purpura in the initial stage of invasive meningococcal infection.[13] Unfortunately, we were not able to include the severity score in our data, although in our study PIIR was associated with the presence of shock in the univariate analysis and strongly associated with admission to ICU in the multivariate analysis. This is in keeping with the literature and it suggests that the severity of the disease is crucial in PIIR determination.

Hospitalization in ICU (OR = 18) and elevated CRP (OR = 1.5) with primary infection were associated with PIIR in multivariate analysis. This suggests that the severity of the primary infection and the intensity of the inflammatory response could be involved in the pathophysiology of PIIR. No non-steroidal anti-inflammatory drugs (NSAIDs) were used in case of PIIR, although the recommendations for symptomatic management of reactive arthritis comprise their use as first-line,[3] and for rheumatic fever, the World Heart Organization recommends that children receive aspirin to relieve the fever and arthritis.[14] This is related to the fact that NSAIDs have been implicated in suppurative complications during invasive infectious diseases,[15] and even when the primary infection is controlled, physicians are generally not in favor of the use of NSAIDs for infections. It would be interesting to carry out a study comparing the efficacy and safety of aspirin or NSAIDs versus corticosteroids in the management of inflammatory reactions.

This historical collection was stopped in 2012, which is a weakness of the present study, because a new medical software was implemented at that time that was not suitable for the extraction of temperature curves. Unfortunately, we could, therefore, not include more recent cases. However, the standard of care was still the same for these diseases and our results were nonetheless suitable for the intended objective.

The retrospective collection of data, and their analysis using archived paper files, could give rise to a classification bias due to loss of information. However, the monocentric aspect allowed us to have an identical mode of data collection for the 2 groups, thus limiting the potential effect of this bias.

The pathophysiology of PIIR is unknow but regarding literature and our results hypothesis could be proposed.

In the present study, having an elevated CRP level during the primary episode was associated with the occurrence of PIIR in multivariate analysis. This is consistent with the study by Goedvolk et al that showed that both the level of leukocytes in the blood and the level of CRP were higher in patients who had inflammatory complications.[16]

More an elevated temperature and the presence of at least one clinical sepsis-like sign were statistically associated with the occurrence of a PIIR in the univariate analysis but not in the multivariate analysis. This could be due to a lack of power in our study.

PIIR manifestations were not associated with the etiological microorganism that is consistent with a mechanism belonging innate immunity. Moreover, some of the clinical manifestations such as systemic inflammation, fever, arthritis, and cutaneous rash are similar to those seen in innate immunity-mediated diseases such as autoinflammatory diseases.

PIIR manifestations were associated with the localization of initial diagnosis: 37 of the 39 PIIR complicated infections of the serous space, such as pleural effusion, septic arthritis, peritonitis, or sanctuary spaces as bacterial meningitis. For PIIR related to meningitis, cases of chronic/recurrent aseptic meningitis following pneumococcal meningitis have been reported. Interestingly, Two studies found that they were associated with the persistence of pneumococcal antigen in the cerebro-spinal fluid, thus suggesting that inflammation is promoted by antigenic persistence in the serous space.[17,18] More Ladeveze et al have shown that humoral adaptative immunity was ineffective and hypothesize that adaptative immunity failure was "balanced" by an innate immunity response directed against a lifeless antigen responsive based on autoinflammatory pathway.[18] In light of these observations on the one hand, and association between pleuropneumonia and CNSI with PIIR in PIIR-restricted analysis (Table S1) on the other hand, we hypothesize that the localization of infections in "sanctuary" spaces (such as serous or cerebrospinal fluid) may be part of PIIR pathophysiology.

Multi-localization of PIIR could be explained by contiguous extension of localized inflammation, such as our cases of infectious peritonitis that exhibited pleural and intra-abdominal effusion. In other cases, such as infectious meningitis with aseptic arthritis and orchitis, PIIR could be explained as a spread of microbial antigens (either disseminated bacteria secondarily sterilized by antibiotic therapy or the dissemination of antigens after bacterial killing), thereby promoting local and systemic inflammation. This hypothesis is supported by post-meningococcal arthritis studies that have detected meningococcal antigen.[19]

Several authors have also evoked other hypothesis as imbalance of the inflammatory reaction between the bacterium, secreting pro-inflammatory agonists, and the immune system.[20]

PIIR were reported in 20% of our cases, which could be related to the genetic backgrounds of the hosts. A number of authors[21] have demonstrated that the variability of the clinical outcome can be explained by interindividual genetic variability.

Recently, specific delayed manifestations have been described for COronaVIrus Diseases 2019, such as PIMS and Kawasaki disease.[1] We hypothesize that this relationship became apparent as a result of the massive exposure of the general population to this new infectious agent. Other PIIR exist in the background noise of infections in the general population, but they are harder to discern.

PIIR are diverse, and conducting a prospective, multicenter study could confirm the frequency and the characteristics of these inflammatory manifestations for these 3 bacteria but also for other agents. A study devoted to the pathophysiology of these reactions could bolster the hypothesis of an imbalance of inflammatory reactions and the lack of specificity depending on the microbial entity for NMII, GASII, and SPII. These studies could be extended to the agent, to pinpoint the involvement of PIIR, that probably require classification regarding the various agents, and probably various pathophysiologies. Thus, a better understanding of these phenomena could improve PIIR management and allow targeted immunotherapy, as proposed for multisystem inflammatory syndrome in children.

As there are probably underestimated and not limited to these 3 bacteria, physician have to be aware of these diagnosis in rebound of severe infectious to not consider exclusively a bacterial resistance or a sur infection in order to propose oriented exploration and treatment in particular unnecessary antibiotic therapy.

5. Conclusion

In this retrospective and monocentric study, we found that PIIR occurred in approximately 20% of invasive infections by SP, NM, or GAS in childhood. These PIIR often resulted in pleural effusion, arthritis, and meningitis, but were not related to the etiologic pathogen. The risk of exhibiting an inflammatory manifestation was greater with a more severe initial infection, with a high degree of biological inflammatory syndrome that could be considered as warning situations. Regarding their frequency and their morbidity, new diagnostic and therapeutic approaches need to be devised in order to improve the management of PIIR and to prevent unnecessary antibiotic administration for these infections. PIIR are also involved in a multitude of different infections including bacterial, viral, mycotic, and parasitic diseases. They are diverse and warrant classification, as well as a better description and understanding of these manifestations, which would improve the diagnosis and management of these infections.

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Contribution to the field statement

Inflammatory manifestations have a major impact on infectious diseases. Some of them are delayed and result in what are called PIIR. PIIR comprise a broad spectrum of manifestations according to the etiologic agent. They are responsible for unnecessary antibiotic administration and prolonged hospitalizations for common invasive bacterial infections in pediatrics. PIIR are

usually attributed to established autoimmune mechanisms, but there are no robust data in this regard that confirm involvement of autoimmunity in most PIIR.

In order to investigate PIIR, without any preconceived notions regarding the involvement of acquired immunity, we chose 3 bacterial invasive childhood infections that are common in France: SP, NM and GASII. One hundred eighty-nine patients were included. Of these, 20.6% developed PIIR, thus suggesting considerable morbidity for this manifestation. In our study, PIIR were not related to the etiologic agent of infection but appeared to be promoted by the severity of the disease, a high degree of inflammation at the onset of the disease, and localization of the infection to a serous space. Consequently, PIIR appear to be due to dysregulation of innate immunity more than autoimmunity. Additional studies are necessary to further explore this hypothesis.

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