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CARACTERISTIQUES EPIDEMIOLOGIQUES, CLINIQUES ET DEVENIR DES ENFANTS ADMIS EN REANIMATION PEDIATRIQUE POUR UNE INFECTION INVASIVE A PNEUMOCOQUE: ETUDE PROSPECTIVE MULTICENTRIQUE DANS L'INTERREGION OUEST

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Président : Madame le Professeur Christèle GRAS LE GUEN

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INTRODUCTION

Streptococcus pneumoniae est une cause majeure de mortalité infantile dans le monde (1, 2). Une infection invasive à pneumocoque (IPD) est définie par la détection de *S. pneumoniae* dans un liquide biologique stérile, tel que le sang, le liquide pleural ou le LCR. Au cours de la dernière décennie, la vaccination anti-pneumococcique conjuguée (PCV) a été introduite dans de nombreux pays. Elle a ciblé initialement 7 des 90 sérotypes pneumococciques connus, puis 10, et enfin 13 d'entre eux (PCV7 avec les sérotypes 4, 6B, 9V, 14, 18C, 19F, 23F, puis PCV10 avec l'ajout des sérotypes 1, 5, 7F en plus, et PCV13, avec les sérotypes 3, 6A, 19A en supplément) (3, 4). De nombreux travaux ont évalué l'impact de cette vaccination sur l'épidémiologie des IPD. Balsells a notamment rassemblé 68 d'entre eux dans sa récente méta-analyse (3). Les variations dans la distribution des sérotypes circulants a été particulièrement surveillée. Ainsi, après l'introduction du PCV7, une diminution de l'incidence globale des IPD a été observée, alors que la proportion d'infections dues à des sérotypes non inclus dans le PCV7 (particulièrement le 19A) était elle en augmentation (3, 5, 6). Puis, avec le remplacement du PCV7 par le PCV13, d'autres sérotypes de remplacement sont apparus (3, 7). Ces études sont fondamentales pour évaluer le bénéfice de la vaccination anti-pneumococcique, et déterminer les cibles des futurs vaccins. Elles ont ainsi montré une augmentation de la prévalence de comorbidités, chez les patients infectés par les sérotypes non inclus dans le PCV13 (5, 6, 8–11). Cependant, elles ont rarement évalué la sévérité clinique des IPD étudiées (admission en réanimation ou non), ni décrit les thérapeutiques dont les patients ont bénéficié, ou leur taux de séquelles. Ceci est lié au design de ces travaux, essentiellement menés par des réseaux de surveillance nationaux du pneumocoque, qui collectent les souches isolées à partir d'hémoculture, de LCR ou de liquide pleural (3, 5, 8, 9, 12). Les informations cliniques sont alors, dans le meilleur des cas, extraites d'un formulaire standardisé envoyé avec la souche, ou obtenues rétrospectivement. Ainsi, très peu d'études ont décrit spécifiquement les patients présentant des IPD sévères, conduisant au décès ou nécessitant une admission en

réanimation (comorbidités, symptômes initiaux, présentation clinique, prise en charge globale, et devenir). Les données pédiatriques sont encore plus rares. A notre connaissance, il n'existe qu'une seule étude récente sur le sujet, réalisée à Taiwan en 2015(13), et décrivant la présentation clinique et le devenir d'enfants admis en réanimation pour IPD. Or la connaissance de ces données est essentielle pour améliorer nos pratiques, tant dans la prise en charge de ces infections sévères que dans leur prévention. En France, en 2014, l'incidence des IPD chez les enfants de moins de 2ans était de 11.4 cas /100 000 avec une couverture vaccinale à 89.3% dans cette population (14).

L'objectif de cette étude observationnelle prospective et multicentrique était de décrire les caractéristiques épidémiologiques, cliniques, la prise en charge et le devenir des patients décédés ou admis en réanimation pédiatrique pour IPD, sur la période de Août 2008 à Janvier 2014, en France, où la vaccination par le PCV7 a été généralisée à tous les enfants de moins de 2 ans en 2006, et remplacée par le PCV13 en 2010 (15).

CONCLUSION

Ce travail est la première étude offrant une description globale des enfants admis en réanimation pour une IPD, après l'introduction de la vaccination anti-pneumococcique conjuguée en France. Même si l'incidence globale des IPD est en diminution dans notre pays (15), nous avons montré que *S. pneumoniae* restait un pathogène majeur. Dans notre travail, il représentait un quart des infections bactériennes sévères communautaires documentées en réanimation pédiatrique. Et sur les 49 cas de notre série, 10 sont décédés (20%), et quatre ont présenté des séquelles sévères à leur sortie de réanimation (8%). Dans la seule étude récente qui étudiait les enfants atteints d'IPD en réanimation, le taux de mortalité était inférieur (6,2%) (13). Mais leur population était différente de la nôtre, avec des patients plus âgés (âge médian à 3,7 ans versus 2,3 ans dans notre étude) et surtout une majorité de pneumopathie (79%). Dans notre étude, la présentation clinique la plus fréquente était la méningite (61%). Nous avons montré que la prise en charge de ces patients pourrait être améliorée. En effet, alors que l'administration de dexamethasone est recommandée avant ou avec la première injection d'antibiotiques dans la méningite à *S. pneumoniae* (16), seulement un tiers de nos patients en a bénéficié dans l'heure suivant la première dose d'antibiothérapie. L'objectif étant pourtant de diminuer les séquelles par une limitation d'une réponse inflammatoire disproportionnée dans l'espace sub-arachnoidien (16). Une mauvaise adhésion à cette recommandation a aussi été montrée dans d'autres études pédiatriques. Degli Atti et al. a notamment rapporté un taux de 59% en 2014 (17). En comparaison, une étude prospective réalisée dans une population adulte, publiée en 2016, montrait que 78% des patients avaient reçu une corticothérapie adjuvante, avant ou avec la première dose d'antibiotique (18). Dans la même étude, l'odds ratio ajusté de l'association entre dexamethasone administrée selon les recommandations, et mauvais devenir était de 0,55 (0,38–0,80). Ce désintérêt des pédiatres pour la corticothérapie adjuvante pourrait être lié au faible niveau de preuve de son bénéfice dans les populations pédiatriques, jusqu'à présent (16, 19, 20). Cependant, nous avons observé dans notre étude, qu'aucun des patients avec

un mauvais devenir n'en avait bénéficié selon les recommandations, contrairement à 42% de ceux avec un bon devenir (p=0.065). Cette constatation associée aux données de nombreuses études chez les adultes montrant son bénéfice (18, 21, 22), nous oblige à être désormais vigilant sur la bonne administration de la dexamethasone, particulièrement chez les patients admis en réanimation. En effet, une réponse inflammatoire disproportionnée ou altérée joue un rôle clé dans la physiopathologie des IPD sévères (23–25). Et l'avenir de leur traitement passera par l'usage de thérapies immunomodulatives, adaptées au profil de réponse inflammatoire de chaque patient (23, 26).

Dans cette population d'IPD sévères, 40% des patients présentaient une comorbidité. Parmi ceux avec un mauvais devenir, cette proportion atteignait 50%. Ces taux sont supérieurs à des études ne retenant comme comorbidité, que les pathologies pour lesquelles l'advisory comittee of immunization de 2013 recommande la réalisation du vaccin anti-pneumococcique polysaccharidique à 23 valences (27). Mais similaire aux 41,6% retrouvés par Gaviria-Agudelo et al., qui avaient retenu tous types de comorbidités, dans leur étude sur les IPD pédiatriques, après introduction du PCV13 (28). De manière plus globale, nos résultats sont cohérents avec les tendances retrouvées dans les grandes études épidémiologiques menées après l'introduction du PCV13. Nous observons une augmentation de la proportion des patients avec comorbidité, et parmi eux, un taux plus élevé d'infections causées par des sérotypes non inclus dans le PCV13 (5, 11, 29, 30). Ce phénomène est expliqué par la diminution des IPD dues aux sérotypes inclus dans le PCV13, remplacés par des sérotypes non inclus dans le vaccin, et ayant un faible potentiel d'invasivité chez les enfants sains. (11, 30).

La force de ce travail a été son caractère prospectif, multicentrique couplé à un recrutement des patients basé sur le caractère de sévérité clinique de leur IPD (admission en réanimation ou décès). Ceci nous a permis d'avoir une description précise de la présentation clinique, de la prise en charge et du devenir de des enfants admis en réanimation pour IPD sévère, en France après l'introduction du PCV. La limite de cette méthode d'inclusion, fut le taux de

données manquantes sur la caractérisation des souches de pneumocoques. Elles n'ont, en effet, pas été envoyées de manière exhaustive au Centre National de Référence du Pneumocoque. La seconde limite de ce travail a été les modalités d'évaluation des séquelles, réalisée sans échelle standardisée, et précocement à la sortie de réanimation. Ce fait explique probablement notre faible taux de séquelle à 10% en cas de méningite. En comparaison une étude autrichienne récente retrouvait 35% de séquelles à long terme, chez des enfants ayant présenté une méningite à pneumocoque (31).

Au total, dans cette étude réalisée à distance de l'introduction du PCV en France, nous avons montré que *S. pneumoniae* restait responsable d'un quart des infections bactérienne sévères communautaires en réanimation pédiatrique. La méningite était le tableau clinique le plus fréquent dans cette série de 49 cas. Nous avons observé que son pronostic pourrait être potentiellement amélioré, avec un meilleur usage de la corticothérapie. Enfin, 40% des patients inclus avaient une comorbidité, et étaient plus souvent infectés par des sérotypes non inclus dans le PCV13. Ceci pose la question du développement de nouveaux vaccins avec plus de valences, et destinés à cette population précise. Au travers des résultats de ce travail, nous avons démontré l'importance de suivre l'évolution des caractéristiques démographiques, clinique et du devenir des enfants atteints d'IPD sévères, afin d'améliorer la prévention de ces infections, ainsi que leur prise en charge.

ARTICLE AU FORMAT PEDIATRIC CRITICAL CARE MEDECINE

TITLE PAGE

TITLE

Epidemiological characteristics, clinical features and outcomes of children with severe pneumococcal disease: a prospective, multicentric population-based study in 15 French districts.

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Streptococcus pneumoniae, invasive pneumococcal disease, pediatric intensive care unit, serotype, corticosteroids, comorbidities

ABSTRACT

Objective We aimed to describe the demographic, the clinical characteristics and the outcome of the pediatric patients that suffered of severe invasive pneumococcal disease (IPD), in a post pneumococcal conjugate vaccine (PCV) era.

Design This multicentric, prospective population-based study was conducted from August 2008 through January 2014.

Setting Six French university tertiary care hospitals on a geographic zone of 15 adjoining districts participated.

Patients All patients, aged from 1 month to 16 years old, admitted in PICU or died of severe bacterial infection (SBI) with detection of *S. pneumoniae* in a sterile fluid aged were included.

Measurements Demographic characteristics, comorbidities, vaccinal status, clinical courses, treatments, outcome and complementary exams results, including serotype and antibiotic susceptibility were collected.

Main Results On 190 patients with a bacterial documented SBI, *S. pneumoniae* represented the second more frequent bacteria identified, with 49 IPD (26%). Ten patients died (20%), four had severe sequelae (8%). 40% of the patients had comorbidities. They were more often infected by non-PCV13 serotypes (78%), in comparison with the patients without comorbidities (35%) (p=0.04). Meningitis was the most frequent type of IPD (n=30, 61%), followed by pneumonia (n=14, 29%) A third of patients with meningitis received dexamethasone within an hour after the first antibiotic injection. 42% of the group of meningitis patients with good outcome received it, whereas none of the group of meningitis patients with bad outcome did (p=0.065).

Conclusions Ongoing monitoring of epidemiological characteristics, clinical features and outcomes of children admitted in PICU for IPD is fundamental to improve their prevention and management. We showed meningitis outcome could possibly be improved by a better use of the adjunctive corticosteroids therapy. The proportion of the patients with comorbidities increased, with patients more often infected by non PCV-13 serotypes: this could incite to develop new vaccines dedicated to them.

ABBREVIATIONS

ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
HUGO	Group of Pediatric University Hospitals in Western France
IQR	Interquartile Range
IPD	Invasive Pneumococcal Disease
IV	Intravenous
NSAID	Non Steroidal Anti-Inflammatory Drugs
PCV	Pneumococcal Conjugate Vaccine
PICU	Pediatric Intensive Care Unit
PMSI	Medical Program of Information System
C3G	Third Generation Cephalosporins
SBI	Severe Bacterial Infection
PPSV	Pneumococcal Polysacharride Vaccine
WBC	white blood cell

INTRODUCTION

Streptococcus pneumoniae is a major cause of life threatening invasive infections in children worldwide (1, 2). Invasive pneumococcal disease (IPD) is defined by the detection of *S. pneumoniae* in a sterile fluid, such as blood, pleural or cerebrospinal fluid (CSF). For the last decade, the pneumococcal conjugate vaccination (PCV) programs were widespread introduced, initially targeting seven (PCV74, 6B, 9V, 14, 18C, 19F, 23F), then ten (PCV 10 also including serotype 1, 5, 7F), or thirteen (PCV 13 also including 3, 6A, 19A) of the over 90 pneumococcal recognized serotypes (3, 4). As Balsells showed in her recent review and meta-analysis on 68 studies (3), many works have assessed the impact of the vaccination on the epidemiology of invasive pneumococcal disease (IPD). The changes in distribution of circulating serotypes of *S. pneumoniae* have been especially evaluated. Thus after the introduction of heptavalent pneumococcal conjugate vaccine, a global decrease of IPD incidence was observed, although the rates of residual IPD caused by non-PCV7 serotypes (particulary 19A) increased (3, 5, 6). And when the PCV13 replaced the PCV7, another serotype replacement occurred (3, 7). These studies were important to evaluate the benefit of the vaccination, and for the development of new vaccine. Moreover, they have shown comorbidities were more prevalent in children with IPD caused by non-PCV13 serotypes (5, 6, 8–11). Nevertheless, these works rarely assessed the severity of the disease presentation (admission in pediatric intensive care unit (PICU) or not), nether describing the type of care provided or the rate of sequelae. Indeed, they were often conducted by a national network of IPD surveillance, that collected pneumococcal isolates from IPD patients (3, 5, 8, 9, 12). The clinical information of IPD patients was, in the better case, extracted from standardized form send with the isolate, and often retrospectively collected. Thus few studies have analyzed the global profile of patients with severe IPD (comorbidities, early clinical presentation, management provided, and outcome). And there is even less data for children. We found only one retrospective monocentric study conducted in Taiwan in 2015, that described clinical features and outcomes of invasive pneumococcal disease in a PICU (13). However

knowledge of these data is essential to improve our practices in the prevention and the management of severe IPD. In 2014, in France, the incidence of IPD in children aged < 2 years was of 11.4 cases /100 000 and 89.3% of the children aged of 2 year old were fully vaccinated (14).

The aim of this multicentric, prospective population-based study was to describe the demographic, the clinical characteristics and the outcome of the pediatric patients admitted or dead before admission in ICU of severe IPD, in the period of August 2008 to January 2014, in France, where the PCV7 was recommended in 2006 for all the children < 2 years and replaced by the PCV 13 in 2010 (15).

MATERIAL AND METHODS

STUDY DESIGN

From August 2008 through January 2014, the Group of Pediatric University Hospitals in Western France (‘HUGO’) included in an observational prospective population-based study, called DIABACT III, all children admitted in PICU or dead before admission of community acquired severe bacterial infection (SBI). For this study we included all patients of DIABACT III that suffered from an IPD.

SETTING

The HUGO group is composed by 6 French university tertiary care hospitals (in Angers, Brest, Nantes, Poitiers, Rennes and Tours) on a geographic zone of 15 adjoining districts. It provides pediatric care for a population of 11 million people and account for 13% of the national pediatric population. The organization of cares in this geographic area called for all children aged from 1 months to 16 years old, and requiring an hospitalization for SBI, to be transferred to one of the 6 University Hospital of the HUGO.

STUDY POPULATION AND IPD CASES

The SBI was defined according the criteria of the international consensus on sepsis in pediatrics (32). The diagnosis of SBI was done on the results of microbiological tests, clinical examination and imagery. In order to assess the exhaustiveness of our study, we used the Medical Program of Information System (PMSI). We screened inside for all patients hospitalized in the PICU of the 6 hospitals during the inclusion periods, those with a SBI diagnosis defined by the group of codes A00 to A09, A30 to A39, B95, B96, G00, G01 and G03. Patients aged from 1 month to 16 years old were included. Patients with isolated viral infection or a nosocomial bacterial infection, defined as a bacterial infection occurring after 48 hours of hospitalization, were excluded. With the cooperation of the reference centers of sudden unexpected death and the emergency departments of each HUGO hospitals, every

case of death at home in a context of fever was screened, and these meeting with criteria of SBI were included.

From the population included in DIABACT III study, we selected all patients with a pneumococcal invasive disease (IPD). IPD was defined as detection of *S. pneumoniae* in blood and/or pleural fluid, and/or cerebrospinal fluid, by bacterial culture, or the detection of *S. pneumoniae* –specific DNA by PCR, or positive reaction of latex agglutionation test or immunochromatography test in CSF.

Clinical syndromes were categorized as meningitis, pneumonia with or without pleural effusion, endocarditis and bacteriemia without focus. Pneumonia was defined as the presence of radiological pneumonia plus positive blood culture, and/or *S. pneumoniae* isolated from pleural fluid culture, and /or positive blood culture or positive tracheal culture plus pneumonia at the autopsy. The presence of empyema for patients with pneumonia was assessed based on radiographic evaluation. In the rest of this article, the term of pneumonia refers to pneumonia with or without effusion. Meningitis required isolation of *S. pneumoniae* in CSF, or positive blood culture associated with clinical diagnosis of meningitis and CSF pleocytosis. Endocarditis was defined by the criteria of the European Society of Cardiology (33). The remaining patients with blood culture positive without other clinical focus were classified as “bacteriemia without focus”

SEROTYPING OF S.PNEUMONIAE

S. pneumoniae was identified by standard microbiology methods in the laboratory of each HUGO hospital. Isolates were serotyped by latex agglutination with antisera provided by Statens Serum Institute (Copenhagen, Denmark) at the National French Reference Center Antimicrobial susceptibility testing for penicillin, amoxicillin and ceftriaxone or cefotaxime was performed. Minimal inhibitory concentration (MIC) breakpoints for CSF *S. pneumoniae* isolates were determined according to Eucast methods with breakpoints for cefotaxime and ceftriaxone as follows: susceptible, MIC $\leqslant$ 0.50 µg/mL, and resistant, MIC > 2 µg/mL, and for

penicillin as follow: susceptible, MIC ⩽ 0.06 µg/mL and high-level resistant, MIC > 2 µg/mL (34).

OUTCOME MEASUREMENTS

For each patient were collected: demographic characteristics, vaccinal status, any ongoing treatment at the start of the management, and any underlying condition. We considered as "completely vaccinated", a patient that had received all the injections of PCV and pneumococcal polysaccharide vaccine (PPSV) 23 recommended by the national vaccination program according his age and comorbidities, at the time of its inclusion in the study. Indeed the French recommendation of pneumococcal vaccination changed during the study, with the shift from PCV7 to PCV13 in June 2010 (without a catch-up program for children 2 to 5 y old), and then with the simplification of the 3 + 1 schedule (2, 3, 4 and 16-18 months) to the 2+1 schedule (2,4 and 11 months) in 2013 (15).

A pre-established template reconstructed for each patient the timed and dated medical observations with signs of severe disease: signs of sepsis (tachycardia, bradycardia, and tachypnea) (32), presence of tonus disorders, impaired vigilance, respiratory distress, or other signs of potential SBI, such as meningism. At any time of the management, the dosage and the timing of administration of any treatment such as antibiotics, corticosteroids, non steroidal anti-inflammatory drugs (NSAID), anti-convulsivant, amines, tracheal tube and extracorporeal membrane oxygenation (ECMO), were reported in the standardized form, as well as the laboratory data, the imagery and the immediate outcome at the PICU discharge. Data were tabulated using Excel (Microsoft, Inc, Redmond, USA).

The project was approved by the institutional review board at the NUH the 7th of May 2009. We followed STROBE guidelines to report this study.

STATISTICAL ANALYSES

Continuous variables were expressed as medians and interquartile ranges (IQR) and the Mann-Whitney test was used. Categorical factors were expressed as percentages, and they were compared using the χ^2 tests. The Fisher's test was used if the expected numbers were <5. Statistical analyses were performed using STATISTICA version 10 software (data analysis software system StatSoft, Inc., 2011).

RESULTS

PATIENTS CHARACTERISTICS

Between August 2008 and January 2014, 262 patients were admitted for SBI in the 6 HUGO hospitals. *S. pneumoniae* represented the second more frequent bacteria identified, with 49 IPD on 190 patients with a bacterial documentation (26%). The median age of the 49 patients included was 28.6 months (IQR 7.4-59.1), 23 of them were male (47%) and 20 had underlying condition (41%) (Table 1). The underlying conditions of the patients included are precisely described in the Supplemental Table 1.

CLINICAL FEATURES

Meningitis was the most frequent type of IPD, (n=30, 61%) followed by pneumonia (n=14, 29%) with effusion (n=10) or without effusion (n=4) (Table 1). The patients with meningitis were younger than those with pneumonia. Indeed 57% versus 14% were aged less than one year, (p=0.025) (Table 2). Any symptom was specific of one kind of clinical presentation, except for seizure, presented only by the patients with meningitis. Of note, influenza virus was found in 5/14 (36%) of the patients with pneumonia. 4/5 of those patients had underlying condition versus 3/9 of the rest of the patients with pneumonia p=0.13. 11/30 (37 %) of the patients with meningitis had acute media otitis, whereas none of those with pneumonia (p=0.007). Their median age was 8.6 months (IQR 7.4-62.1 months) and 63% of them had positive blood culture, versus 58% of the patients with meningitis without otitis p=0.53. The time between the first medical consultation and the admission in PICU was four time shorter for the patients with meningitis in comparison of those with pneumonia, median of 24 hours (IQR 6-46h) versus 93h (IQR 50-174), p=0.002. But the length of stay in PICU was not significantly different between the two groups (Table 2).

PATIENTS OUTCOMES

On 49 patients ten died (20%), and four (8%) had severe sequelae at the discharge of PICU (Table 3). The differences in clinical features and treatments received, according the outcome, are presented in the table 1. Among the 6 patients having meningitis in the group with poor outcome, the median of time between the antibiotics injection and dexamethasone administration was 240 minutes (IQR 75-480 minutes). In comparison, 42% of the patients with meningitis of the group without sequelae received dexamethasone within 1 hour (p=0.065). And the median of time between antibiotics administration and dexamethasone injection in this group was 60 minutes (IQR 0-105 min, p=0.055).

THERAPIES ACCORDING THE CLINICAL PRESENTATION

The NSAID were more used in pneumonia than in meningitis, 57% versus 20% p=0.018 (Table 4). For meningitis the antibiotic treatments prescribed in PICU were almost intravenous (IV) bitherapy with third generation cephalosporins (C3G) associated with vancomycin (Table 4 and supplemental table 2). For pneumonia, C3G associated with rifampin or vancomycin were administrated in 57% of the cases. The median dose of cefotaxime was 300mg/kg/d (IQR 300-300) for patients with meningitis, and 200 mg/kg/d for patient with empyema (IQR 200-200) (Supplemental table 3). In case of meningitis, the dose of vancomycin prescribed in the emergency department or general pediatric unit was a lower than the dose prescribed in PICU, 23mg/kg/d (IQR 15-40) versus 60 mg/kg/d (IQR, 40-60), p<0.01.

PNEUMOCOCCAL ISOLATES

The serotype of the isolates was available for 73% of the patient with meningitis (Table 2). In case of pneumonia, it was available for 5 isolates (36%). Even all patients with pneumonia beneficiated of at least one blood culture, only 4 patients of them had a positive one (29%), whereas 64% of the patient with meningitis (p =0.03). For the patients with meningitis, 54% of the serotypes identified were not covered by the PCV13 (Fig. 1).

On the 4 penicillin-resistant *Streptococcus pneumoniae* isolated in this work, two were serotype 19A, and the two others were serotype 19F (Table 2). All of them were C3G sensible with a CMI of cefotaxime at 0.5 mg/L. Two patients infected by PRSP had poor outcome (Table 3).

Of note in the 29 patients with a serotype identified, non-PCV13 serotypes were found in 7/9 (78%) patients with underlying condition, in comparison with 7/20 (35%) of the patient without comorbidities (p=0.04). And on the 44 patients with a vaccinal status available, the proportion of patients completely vaccinated was not significant different between the patients with comorbidities 12/16 (75%) and those without 17/28 (61%) (p=0.27).

Table 1 Clinical features and treatments of IPD patients admitted in PICU by outcome status

Variable n (%), median [IQR], (/n=number of available answers if different of N =)	Total N=49	Surviving without sequelae N=35	Severe sequelae or died N=14	p
Age (months)	28.63 [7.42-59.12]	34.1 [7.0-62.1]	23.5 [7.5-37.5]	0.56
Male	23 (47)	15 (43)	8 (57)	0.28
Comorbidity ≥ 1	20 (41)	13 (38)	7 (50)	0.31
Completely vaccinated	29/44 (66)	24/31 (77)	5/13 (38)	0.017
Final diagnosis				
Meningitis	30 (61)	24 (69)	6 (43)	0.003
Pneumonia with/without effusion	14 (29)	11 (31)	3 (21)	
Endocarditis	1 (2)	0	1 (7)	
Bacteriema without other focus	4 (8)	0	4 (9)	
Number of consultations	3 [2-4]	3 [2-4]	2.5 [1-4]	0.54
Time between admission in ICU and				
First medical consultation (h)	33.9 [7.5-87] (n=46)	40.5 [6.2-74.1] (n=35)	27.3 [8-214.9] (n=11)	0.32
Clinical presentation				
Fever as first symptom	46 (94)	34 (97)	12 (86)	0.19
Maximal temperature (°C)	39.5 [39-40] (n=40)	39.5 [39-40] (n=31)	40 [39-40] (n=9)	0.56
Seizure	9 (18)	7 (20)	2 (14)	0.49
DIC	3 (6)	1 (3)	2 (14)	0.19
Cardiopulmonary rescusitation	5 (10)	0	5 (36)	0.001
PRISM score	2 [0-8] (n=38)	1.5 [0-5.5] (n=28)	13.5 [0-31] (n=10)	0.037
Laboratory values at the admission in ICU				
WBC (cells/mm³)	16130 [6180-18920] (n=27)	17395 [11120-18920] (n=18)	4600 [4000-8970] (n=9)	0.023
CRP (mg/L)	163 [110-264] (n=31)	163 [77-264] (n=23)	166 [121-188] (n=8)	0.87
PCT (µg/L)	24.25 [3.3-47.5] (n=22)	14.66 [2.5-41.4] (n=14)	39.75 [6.4-162.5] (n=8)	0.26
Lactates (mmol/L)	1.7 [1.2-2.7] (n=35)	1.4 [1.1-2.1] (n=25)	2.7 [1.9-4.4] (n=10)	0.004
Treatments				
Tracheal tube	19 (39)	9 (26)	10 (71)	0.004
ECMO	2 (4)	0	2 (14)	0.077
Amines	11 (22)	3 (9)	8 (57)	0.0007
Meningitis received dexamethasone within 60 min	10/30	10/24 (42)	0/6	.065
ICU lenght of stay (h)	98 [1-2616] (n=45)	97 [67-147] (n=32)	116 [1-2616] (n=13)	0.93

Abbreviations : DIC, disseminated intravascular coagulation ; ECMO, extracorporeal membrane oxygenation ; ICU, intensive care uni t; IPD, invasive pneumococcal disease; IQR, interquartile range ; WBC, white blood cell;

Table 2 Comparison of demographic characteristics, serotype distribution, and outcomes of IPD patients with meningitis and pneumonia with/ without effusion

Variable n (%), median [IQR] (/ n=number of available answers if different of N =)	Meningitis N=30	Pneumonia with/without effusion N=14	p
Comorbidity	10 (33)	7 (50)	0.23
Age			
< 12 months	17 (57)	2 (14)	0.024
12 to 59 months	6 (20)	7 (50)	
> 59 months	7 (23)	5 (36)	
Serotype distribution			
PCV 7 serotypes	4 (13)	2 (14)	0.11
PCV 13 minus PCV7 serotypes	6 (20)	2 (14)	
PPSV 23 minus PCV13 serotypes	6 (20)	1 (7)	
other serotypes	6 (20)	0	
NA	8 (27)	9 (64)	
Antibibiotic sensitivity			
PSSP	17 (57)	4 (29)	0.15
PSDP	3 (10)	1 (7)	
NA	10 (33)	9 (64)	
Streptococcus pneumoniae detected in			
CSF culture	24 (80)	0	<0.001
Blood culture	21 /28[a] (60)	4/14[a] (29)	
Pleural fluid culture	0	6 (43)	
PCR (performed on any fluid)	2 (7)	1 (7)	
Others	0	2 (14)	
NA	1 (3)	3 (21)	
Several bacterial cultures	14 (47)	2 (14)	
Clinical presentation			
Fever	28 (93)	13 (93)	0.69
Tachycardia	17 (57)	10 (71)	0.28
Hypotension	3 (10)	1 (7)	0.62
Polypnea	15 (64)	9 (50)	0.289
Neurologic signs[b]	29 (97)	7 (50)	<0.001
Seizure	9 (30)	0	0.020
Cought	4 (13)	9 (64)	0.001
Vomiting	4 (13)	2 (14)	0.63
Time between first medical consultation and admission in ICU (h)	24 (6-46)	93 (50-174)	0.002
ICU lenght of stay	96 [16-787] (n=29)	120 [1-408] (n=11)	0.81

[a]number of patients with blood culture performed
[b]neck stiffness and/or focal neurologic deficit and/or headache and/or disturbed consciousness and/or complaints
Abbreviations : CSF, cerebrospinal fluid ; IQR, interquartile range ; NA, not available ; PCV 7 or 13, heptavalent or 13-valent pneumococcal conjugate vaccine ; PPSV23, 23 valent pneumococcal polysaccharide vaccine ; PSSP, penicillin-sensitive *Streptococcus pneumoniae; PRSP,* penicillin-resistant *Streptococcus pneumoniae,* WBC, white blood cell

Table 3 Description of IPD patients died or with severe sequelae at the PICU discharge

Case	Age, months	Gender	Comorbidity	Fully vaccinated	Clinical diagnosis	Serotype	Penicillin Sensitivity	Dexamethasone [a]	Outcome
1	8	male	No	no	meningitis with osteoarthritis of the right hip	19A	PRSP	no	hydrocephalus, ventriculoperitoneal shunt, epilepsy, hearing loss, vision loss, cognitive impairment
2	36	male	language delay	no	meningitis	15 B	PSSP	yes (480 min)	died after end-of-life decision because of severe intracranial hypertension, severe basal ganglia lesions and vascularitis of the brainstem
3	7	female	severe head injury	no	meningitis	non typable	PSSP	no	died of brain herniation followed by cardiac failure and brain death
4	20	male	13q deletion syndrome and Hirschsprung disease	yes	bacteriema[b]	NA	NA		died of septic shock leading to cardiac arrest
5	4	female	no	no	meningitis	23F	NA	no	died of severe brain injury
6	2	male	no	yes	meningitis	9N	PSSP	yes (240 min)	left arm monoplegia
7	2	female	Jeune asphyxiating thoracic dystrophy	no	pneumonia without effusion on post-mortem	17F	PSSP		died before the hospital admission
8	37	male	growth retardation	no	pneumonia without effusion on post-mortem	NA	NA		died before the hospiltal admission
9	9	male	no	yes	endocarditis	NA	NA		died after end-of-life decision because of multiple organ failure
10	29	male	myopathy, tracheotomy	NA	bacteriema[b]	NA	NA		died of multiple organ failure
11	156	female	Wiskott-Aldrich syndrome	yes	bacteriema[b]	22F	PSSP		died of multiple organ failure
12	192	female	no	yes	meningitis	19F	PRSP	yes (75 min)	cognitive impairment, mutism, flaccid paralysis
13	40	male	no	no	bacteriema[b]	7F	PSSP		severe neurologic sequelae after cardiopulmonary resuscitation, 15 days of ECMO and 2 months of mechanical ventilation and amines.
14	26	female	no	no	pneumonia with effusion	NA	PSSP		Died after end-of-life decision, on ECMO after a surgey for bronchopulmonary fistula complicated severe brain injuries

[a] yes/no in case of meningitis and time between antibiotic administration and dexamethasone injection (minutes),[b] bacteriema without other focus
Abbreviations : ECMO, extracorporeal membrane oxygenation ; NA, not available ; PSSP, penicillin-sensitive Streptococcus pneumoniae; PRSP, penicillin-resistant Streptococcus pneumoniae

Table 4 Comparison of the therapies received by severe IPD patients hospitalized in PICU for meningitis and pneumonia with/without effusion patients

Variable n (%), median [IQR]	Meningitis	Pneumonia with/without effusion
Antibiotherapy		
First lign in GP¨/ED		
Monotherapy	16 (53)	6 (43)
Bitherapy	11 (37)	6 (43)
Tritherapy	3 (10)	0
NA	0	2 (14)
First lign in PICU		
Monotherapy	11 (37)	4 (29)
Bitherapy	13 (43)	8 (57)
Tritherapy	6 (20)	1 (7)
NA	0	1(7)
Second lign of antibiotherapy prescribed in PICU	4 (13)	4 (29)
Amines	3 (10)	4 (29)
Norepinephrine	3 (11)	4 (31)
Epinephrine	1 (3)	1 (7)
Dobutamine	1 (3)	1 (7)
Corotrope	1 (3)	0
Dexamethasone	20 (67)	0
Dexamethasone dose mg/kg/d	0.6 [0.6-0.6]	
Non steroidal anti inflammatory drugs	6 (20)	8 (57)
Anticonvulsant	11 (37)	0
ECMO	0	1 (7)
Tracheal tube	11 (37)	4 (29)
Lenght of tracheal tube	4 [2-8] (n=11)	1 [1-18] (n=3)

Abbreviations : ECMO, extracorporeal membrane oxygenation ; PICU, pediatric intensive care uni t; IQR, interquartile range ; NA, not available

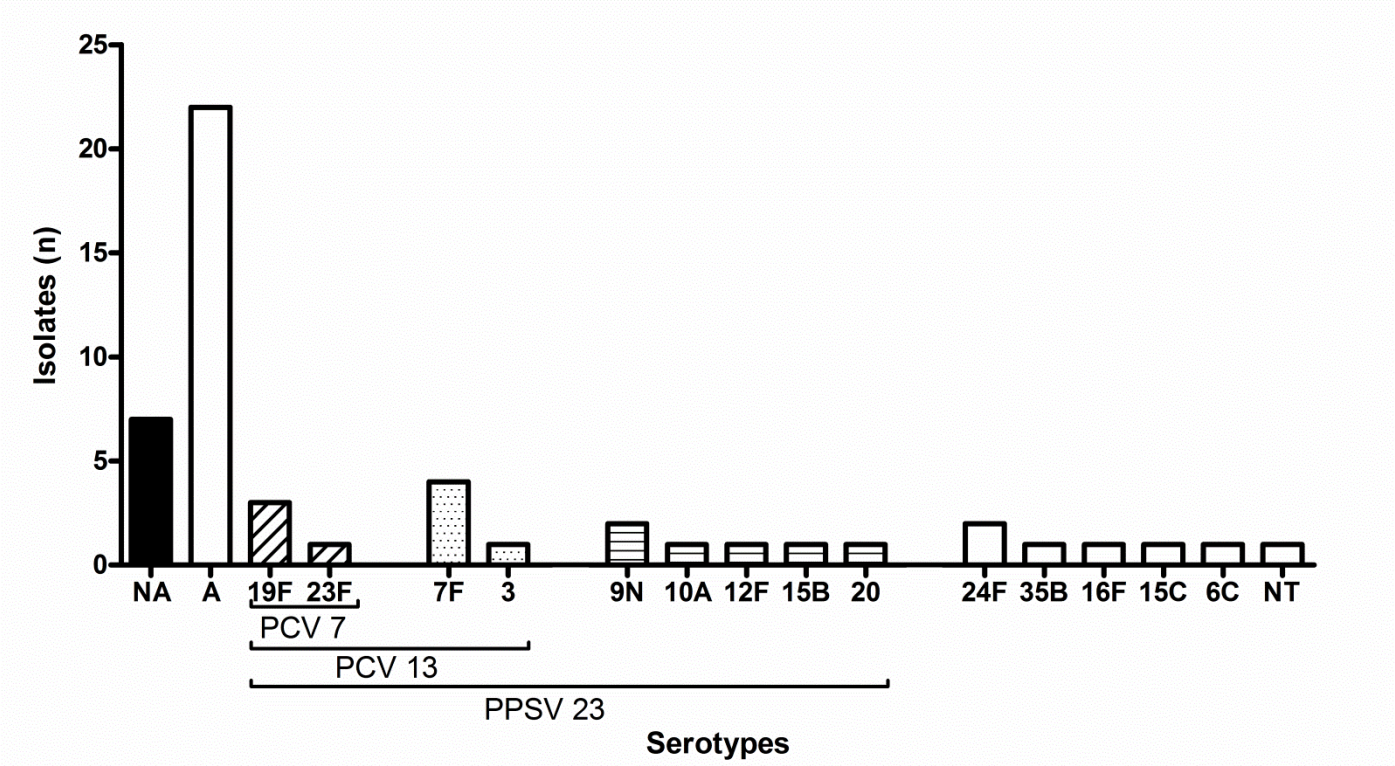

Figure 1 Distribution of the serotypes of the pneumococcal isolates, grouped by vaccine serotype, from patients with meningitis hospitalized in PICU; from 15 French districts, between August 2008 to January 2014

Abbreviations: A, available ; NA, not available ; NT, non typable ; PCV pneumococcal conjugate vaccine ; PPSV, pneumococcal polysaccharide vaccine.

DISCUSSION

This is the first French study providing a detailed description of severe IPD in PICU, after the introduction of the PCV vaccination for all the children < 2 years (PCV 7 in 2006, replaced by PCV 13 in 2010). We showed *S. pneumoniae* was still responsible of a quarter of the documented IBS leading children in PICU, even if Le Poutre et al. observed a global decrease of all-type IPD in children <15 years from 40.3 to 25.1 cases / 100 000 population, between 2001 and 2012, in France (15).

In this series of 49 severe IPD cases, ten patients died (20%). As expected this rate is higher than in studies assessing global IPD fatality rate in children. For example, Cohen et al. had a global mortality rate of 9% in case of meningitis in children <18 years between 2011-2014 in France (30). We found the highest case fatality rate among patients with bacteriemia without other focus (3/4 patients died), as in the study of Backhaus and al.(35). At the best of our knowledge the only other recent study assessing IPD in PICU was realized by Hsiao et al. in Taiwan (13). They had a low mortality rate of 6.2 %. But their recruitment was different, with patients older (median age 3.7 years versus 2.3 years in ours work) and a majority of pneumonia (79%). In contrast, the more frequent clinical presentation in your work was meningitis (61%). Pneumonia with or without effusion represented only 29% of the cases. These proportions of clinical syndromes are inversed in comparison with the global data of IPD in France. Thus in 2012 the incidence of pneumococcal meningitis was of 5.3 cases /100 000 children < 15 years and of 19.3/100 000 for the others IPD (15).This difference reflects the severity of the disease in meningitis, which affects younger, so more vulnerable, children than pneumonia (35). Nevertheless, our management of meningitis could be improved. Indeed, even dexamethasone is recommended in pneumococcal meningitis, in order to reduce the inflammatory response in the subarachnoid space in view to improve the outcome (16). Only a third of the patients with meningitis in our study received it within an hour after the first antibiotic injection. The adherence to its use was suboptimal in other pediatrics studies. Degli Atti et al. had a rate of 59% (17). In comparison a prospective study published

last year in adults, showed 78% of the patients received dexamethasone before or with the first dose of IV antibiotics (18). And in the same study the adjusted odds ratio for the association between dexamethasone treatment according the guidelines and unfavorable outcome in patients with pneumococcal meningitis was 0·55 (0·38–0·80). These disinterest of the pediatricians for of adjunctive corticosteroids therapy may be linked to the weak level of evidence of its benefit in pediatrics (16, 19, 20). However we observed in our study that none meningitis patients with bad outcome had received dexamethasone: within 60 minutes after the administration of antibiotic therapy, whereas 42% of the patients with good outcome did (p=0.065). This result, associated with the more and more evidences brought by studies in adults (18, 21, 22), forces us to take this matter seriously up to now, especially for the severe cases admitted in ICU. Indeed we know the disproportionate or altered inflammatory response plays a key role in severe IPD (23–25). And the future is in immunomodulative therapy, like corticosteroids, adapted to each patient, in function to his cluster of inflammatory response(23, 26). On this point we showed the patients with bad outcome had significant lower rate of white blood cell (WBC) at the admission in ICU, in comparison of those with a good outcome, median at 4600 cells/mm^3 versus 17395 cell/mm^3 (p=0.023). Similarly Hanada et al. demonstrated that WBC count <4000 cells/µL was associated, with an odds ratio of 6.9 (IC95% 3.7–12.8), with the mortality in adults IPD(36). This result has to be confirmed in a prospective study assessing the kinetic of different markers of the inflammatory response in the pediatric patients with severe IPD.

We also demonstrated patients with pneumonia had received more often NSAID than those with meningitis. It is tricky to formulate conclusion from this fact. Indeed the patients with pneumonia had a longer timing between the first medical consultation and their admission in ICU 93h versus 24h (p=0.002). So they had more chances to benefit of a prescription of NSAID as antipyretic drug. Several studies have shown an association between NSAID and complicated pneumonia (37–39), but all concluded further searches are needed in order to

investigate the exact role of NSAID use in modulating the course of disease in children with pneumonia (37, 38).

In this population of severe IPD, 40% of the patients had underlying condition, and this rate raised 50% for the patients with bad outcome. This rate is superior than those of studies that only retained the medical condition consistent with the 2013 advisory committee on immunization as comorbidities(27). But similar to the 41.6% found by Gaviria-Agudelo et al. that recorded all kind of underlying condition in their study on pediatric IPD in a post PCV 13 era (28). For the rest, our results are consistent with the last trends showed in epidemiological studies in post-PCV13 era. We observed an increase of the proportion of patients with comorbidities, and among them a higher rate of IPD caused by non-PCV13 serotypes(5, 11, 29, 30). The phenomenon is explained by the decrease of the IPD due to PCV13 serotypes, replaced by non-PCV13 serotypes that have a low potential of invasiveness in healthy children(11, 30). In your study we had no isolate with a cefotaxime CMI > 0.5 mg/L, it corresponds to the French national data on *S. pneumoniae* sensibility(15). In this context the vancomycin is no more recommended in first line in the pediatric pneumococcal meningitis since 2014 (40).

The strength of our study is a prospective, multicentric design, coupled with a recruitment based on the severity of the disease presentation (death or admission in PICU). That permitted us to have a precise description of the clinical presentation and the management of severe pediatric IPD in the French post PCV-13 era. These data are important to adapt our pneumococcal vaccination program, especially for the patients with underlying condition. The limit of this mode of inclusion was the missing data concerning the pneumococcal isolates, which were non-exhaustively sent to National French Reference Center of *S. pneumoniae*. Globally Cohen et al. had the same rate of serotype identification of 73% in their study on pneumococcal meningitis in children in France published in 2016 (30). But for pneumonia our rate of 36% of serotype identification was low. The second limit of this work is the modality of evaluation of the sequelae. They were only assessed at the

discharge of PICU without using the Glasgow outcome scale. This probably explains our low rate of sequelae of 10% in case of meningitis, in comparison with the 35% of long term sequelae found in a recent Austrian series of pediatric pneumococcal meningitis cases(31). In this study there were 7.5% of motor disorder, 2.5% of speech disorder and 22.5% of hearing loss.

CONCLUSION

Our study, in a post-PCV13 era, showed that *S. pneumoniae* was still responsible of a quarter of the severe bacterial infection in PICU. Meningitis was the more frequent clinical syndrome of severe IPD, in this series of 49 cases. We demonstrated its outcome could possibly be improved by a better use of the adjunctive corticosteroids therapy. Lastly, 40 % of the patients with severe IPD had comorbidities, and they were more often infected by non PCV-13 serotypes. This could incite to develop new vaccines dedicated to these children with comorbidities and including more serotypes. Ongoing monitoring of epidemiological characteristics, clinical features and outcomes of children admitted in PICU for IPD is fundamental to improve their prevention and management.

REFERENCES

1. O'Brien KL, Wolfson LJ, Watt JP, et al.: Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *The Lancet* 2009; 374:893–902

2. Liu L, Oza S, Hogan D, et al.: Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *The Lancet* 2015; 385:430–440

3. Balsells E, Guillot L, Nair H, et al.: Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. *PLOS ONE* 2017; 12:e0177113

4. Htar MTT, Christopoulou D, Schmitt H-J: Pneumococcal serotype evolution in Western Europe. *BMC Infect Dis* 2015; 15:419

5. Tam P-YI, Madoff LC, Coombes B, et al.: Invasive Pneumococcal Disease After Implementation of 13-Valent Conjugate Vaccine. *Pediatrics* 2014; 134:210–217

6. Yildirim I, Shea KM, Pelton SI: Pneumococcal Disease in the Era of Pneumococcal Conjugate Vaccine. *Infect Dis Clin North Am* 2015; 29:679–697

7. Savulescu C, Krizova P, Lepoutre A, et al.: Effect of high-valency pneumococcal conjugate vaccines on invasive pneumococcal disease in children in SpIDnet countries: an observational multicentre study. *Lancet Respir Med* 2017; S2213-2600(17)30110-8

8. Ladhani SN, Slack MPE, Andrews NJ, et al.: Invasive Pneumococcal Disease after Routine Pneumococcal Conjugate Vaccination in Children, England and Wales. *Emerg Infect Dis* 2013; 19:61–68

9. Browall S, Backhaus E, Naucler P, et al.: Clinical manifestations of invasive pneumococcal disease by vaccine and non-vaccine types. *Eur Respir J* 2014; 44:1646–1657

10. Cohen R, Biscardi S, Levy C: The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. *Hum Vaccines Immunother* 2016; 12:277–284

11. Yildirim I, Shea KM, Little BA, et al.: Vaccination, Underlying Comorbidities, and Risk of Invasive Pneumococcal Disease. *PEDIATRICS* 2015; 135:495–503

12. Maurice A de S, Grijalva CG, Fonnesbeck C, et al.: Racial and Regional Differences in Rates of Invasive Pneumococcal Disease. *Pediatrics* 2015; 136:e1186–e1194

13. Hsiao H-J, Wu C-T, Huang J-L, et al.: Clinical features and outcomes of invasive pneumococcal disease in a pediatric intensive care unit. *BMC Pediatr* 2015; 15:85

14. Centre National de Référence des Pneumocoques. Rapport d'activité 2015. Available from: http://cnr-pneumo.com. Accessed May 26, 2017

15. Lepoutre A, Varon E, Georges S, et al.: Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001–2012. *Vaccine* 2015; 33:359–366

16. Saux NL, Society CP, Committee ID and I: Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age. *Paediatr Child Health* 2014; 19:141

17. Atti MC degli, Esposito S, Parola L, et al.: In-hospital management of children with bacterial meningitis in Italy [Internet]. *Ital J Pediatr* 2014; 40[cited 2017 May 27] Available from: https://www-ncbi-nlm-nih-gov.passerelle.univ-rennes1.fr/pmc/articles/PMC4247725/

18. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al.: Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 2016; 16:339–347

19. McGill F, Heyderman RS, Panagiotou S, et al.: Acute bacterial meningitis in adults. *The Lancet* 2016; 388:3036–3047

20. Mongelluzzo J, Mohamad Z, Ten Have TR, et al.: Corticosteroids and mortality in children with bacterial meningitis. *JAMA* 2008; 299:2048–2055

21. Buchholz G, Koedel U, Pfister H-W, et al.: Dramatic reduction of mortality in pneumococcal meningitis. *Crit Care* 2016; 20:312

22. Glimåker M, Brink M, Naucler P, et al.: Betamethasone and dexamethasone in adult community-acquired bacterial meningitis: a quality registry study from 1995 to 2014. *Clin Microbiol Infect* 2016; 22:814.e1-814.e7

23. Nau R, Djukic M, Spreer A, et al.: Bacterial meningitis: an update of new treatment options. *Expert Rev Anti Infect Ther* 2015; 13:1401–1423

24. Fernandez-Botran R, Uriarte SM, Arnold FW, et al.: Contrasting Inflammatory Responses in Severe and Non-severe Community-acquired Pneumonia. *Inflammation* 2014; 37:1158–1166

25. Bordon J, Aliberti S, Fernandez-Botran R, et al.: Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. *Int J Infect Dis* 2013; 17:e76–e83

26. Liechti FD, Grandgirard D, Leib SL: Bacterial meningitis: insights into pathogenesis and evaluation of new treatment options: a perspective from experimental studies. *Future Microbiol* 2015; 10:1195–1213

27. CDC. Vaccine Information Statement Pneumococcal Polysaccharide. Available from: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/ppv.html. Accessed May 28, 201l

28. Gaviria-Agudelo CL, Jordan-Villegas A, Garcia C, et al.: The Effect of 13-Valent Pneumococcal Conjugate Vaccine on the Serotype Distribution and Antibiotic Resistance Profiles in Children With Invasive Pneumococcal Disease. *J Pediatr Infect Dis Soc* 2016; piw005

29. Ladhani SN, Andrews NJ, Waight P, et al.: Invasive pneumococcal disease, comorbidities, and polysaccharide vaccine use in children aged 5-15 years in England and Wales. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2014; 58:517–525

30. Cohen R, Varon E, Béchet S, et al.: Comparative impact of pneumococcal conjugate vaccines on pneumococcal meningitis according to underlying conditions. *Vaccine* 2016; 34:4850–4856

31. Klobassa DS, Zoehrer B, Paulke-Korinek M, et al.: The burden of pneumococcal meningitis in Austrian children between 2001 and 2008. *Eur J Pediatr* 2014; 173:871–878

32. Goldstein B, Giroir B, Randolph A: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*. *Pediatr Crit Care Med* 2005; 6:2–8

33. Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer, Authors/Task Force Members, Habib G, et al.: Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* 2009; 30:2369–2413

34. EUCAST. Clinical breakpoints. Available from: http://www.eucast.org/clinical_breakpoints. Accessed May 26, 2017/

35. Backhaus E, Berg S, Andersson R, et al.: Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. *BMC Infect Dis* 2016; 16:367

36. Hanada S, Iwata S, Kishi K, et al.: Host Factors and Biomarkers Associated with Poor Outcomes in Adults with Invasive Pneumococcal Disease. *PLOS ONE* 2016; 11:e0147877

37. Voiriot G, Dury S, Parrot A, et al.: Nonsteroidal Antiinflammatory Drugs May Affect the Presentation and Course of Community-Acquired Pneumonia. *Chest* 2011; 139:387–394

38. Elemraid MA, Thomas MF, Blain AP, et al.: Risk factors for the development of pleural empyema in children. *Pediatr Pulmonol* 2015; 50:721–726

39. Le Bourgeois M, Ferroni A, Leruez-Ville M, et al.: Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. *J Pediatr* 2016; 175:47–53.e3

40. Levy C, Varon E, Taha M-K, et al.: [Changes in bacterial meningitis in French children resulting from vaccination]. *Arch Pediatr Organe Off Soc Francaise Pediatr* 2014; 21:736–744

Supplemental table 1 Detailed comorbidities according the outcome of 49 severe IDP patients hospitalized in PICU

Variable n (%), median [IQR]	Total N=49	Surviving without sequelae N=35	Severe sequelae or died N=14
comorbidity ≥ 1	20 (41)	13 (38)	7 (50)
number of comorbidity	1 [1-4]	1 [1-2]	1 [1-3]
history of severe bacterial infection	9	7	2
prematurity < 37 SA	5	5	0
growth retardation	3	1	2
chronic neurological disease	4	3	1
severe Head Injury	3	2	1
developmental delay	2	1	1
congenital heart disease	1	1	0
other malformation	2	1	1
asthma	1	1	0
immunodeficiency	1	0	1
13q deletion syndrome	1	0	1
Hirschsprung disease	1	0	1

Abbreviations : IPD, invasive pneumococcal disease ; IQR, interquartile range ; PICU, pediatric intensive care unit

Supplemental table 2 Type of antibiotherapy prescribed to severe IPD patients with meningitis or pneumonia with/without effusion, in emergency or general pediatric unit and in PICU.

	Meningitis		Pneumonia with/without effusion	
	ED/GP unit	PICU	ED/GP unit	PICU
Variable n (%)	n=30	n=30	n=14	n=14
Monotherapy	16 (53)	11 (37)	6 (43)	2 (14)
amoxicillin	1	0	1	0
amoxicillin clavulanic	0	0	1	0
C3G PO	2	0	0	0
C3G IV	13	5	4	2
Glycopeptide	0	6[a]	0	0
Bitherapy	11 (37)	12 (40)	6 (43)	10 (72)
amoxicillin + macrolide	0	0	1	0
amoxicillin + rifampin	0	1	0	0
amoxicillin + C3G	0	1	0	0
C3G + rifampin	0	0	4	5
C3G + glycopeptide	8	9	0	3
C3G + aminoglycoside	3	1	1	0
C3G + sulfamide	0	0	0	1
macrolide + glycopeptide	0	0	0	1
Tritherapy	3 (10)	6 (20)	0	1 (7)
C3G + amoxicillin clavulanic + aminoglycoside	0	0	0	1
C3G+ cloxacillin + aminoglycoside	0	0	0	0
C3G + glycopeptide + aminoglycoside	3	5	0	0
C3G + fosfomycin + metronidazole	0	1	0	0
Quadritherapy	0	1 (3)	0	0
C3G + glycopeptide + aminoglycoside + metronidazole	0	1	0	0
NA	0	0	2 (14)	1 (7)

[a]Only glycopeptides were reported in the form, but all of these patients received beta-lactams antibiotics in ED/GP (4 C3G IV, 1 C3G PO, 1 amoxicillin).
Abbreviations : IPD, invasive pneumococcal disease ; PICU, pediatric intensive care unit ; ED, emergency department ; GP, general pediatric unit ; C3G, cephalosporin third generation

Supplemental table 3 Dosage of the first line of antibiotic therapy prescribed in general pediatric unit or emergency department and in PICU, in case of severe IPD.

	All IPD (N=49)				Meningitis (N=30)				Empyema (N=10)			
	ED/GP unit		ICU		ED/GP unit		ICU		ED/GP unit		ICU	
	n[a]	dose, mg/kg/d, median [IQR]	n[a]	dose, mg/kg/d, median [IQR]	n[a]	dose, mg/kg/d, median [IQR]	n[a]	dose, mg/kg/d, median [IQR]	n[a]	dose, mg/kg/d, median [IQR]	n[a]	dose, mg/kg/d, median [IQR]
cefotaxime	23/25	200 (85-300)	32/34	300 (200-300)	16/16	290 (200-300)	20/20	300 (300-300)	5/6	185 (150-200)	8/9	200 (200-200)
ceftriaxone	14/14	50 (50-93)	5/6	50 (50-100)	11/11	50 (50-93)	3/3	50 (50-100)	1/1	50	1/1	50
vancomycin	13/13	23 (15-40)[b]	26/28	60 (40-60)[b]	11/11	23 (15-40)[b]	20/20	60 (45-60)[b]	0	0	3/3	40 (30-41.5)
gentamycin	6/6	3 (3-3)	7/9	3 (3-4,5)	5/5	3 (3-3)	5/5	3 (3-4.5)	0	0	0	
rifampin	4/5	20 (19.3-20)	5/7	18.6 (15-20)	0		0	0	3/4	20 (18,6-20)	4/5	19.3 (14.3-20)

[a] number of available dose/number of patient receving the antibiotic
[b] p<0.01
Abbreviations :P ICU, pediatric intensive care unit ; IPD, invasive pneumococcal disease, ED, emergency department ; GP, general pediatric unit ; IQR, interquartile range

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Titre de Thèse : CARACTERISTIQUES EPIDEMIOLOGIQUES, CLINIQUES ET DEVENIR DES ENFANTS ADMIS EN REANIMATION PEDIATRIQUE POUR UNE INFECTION INVASIVE A PNEUMOCOQUE : ETUDE PROSPECTIVE MULTICENTRIQUE DANS L'INTERREGION OUEST

RESUME

Cette étude observationnelle prospective et multicentrique, menée entre 2008 et 2014, décrit les caractéristiques épidémiologiques, cliniques, les thérapeutiques reçues, et le devenir des enfants décédé ou admis en réanimation pour une infection invasive à pneumocoque Sur 49 patients inclus, 10 décédèrent. 40% des patients avaient une comorbidité. Ils étaient plus souvent infectés avec des sérotypes non inclus dans le vaccin conjugué à 13 valences (78%, p=0.04). 42% des patients présentant une méningite avec un bon devenir avaient reçu de la dexamethasone dans l'heure suivant le début de l'antibiothérapie, versus aucun de ceux avec un mauvais devenir (p=0.065). Le pronostic des méningites sévères à pneumocoque peut potentiellement être amélioré par un meilleur usage de la corticothérapie. Une vaccination spécifique pourrait être développée pour les patients avec comorbidité.

MOTS-CLES

***Streptococcus pneumoniae*, infection invasive à pneumocoque, réanimation pédiatrique, sérotype, corticostéroïdes, comorbidité**