UNIVERSITÉ DE NANTES

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FACULTÉ DE MÉDECINE

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Année : 2020 N°

THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

DES DE PÉDIATRIE

par

Lucile GESTIN
Née le 18 octobre 1991 à Quimper

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Présentée et soutenue publiquement le 16 mars 2020

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Impact de la mise en place en 2015 du protocole simplifié d'antibiothérapie sur la prescription de céphalosporines de 3ème génération dans les pleuro-pneumopathies de l'enfant au CHU de Nantes : étude PLEURANTIB.

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COMPOSITION DU JURY

Président du jury : Madame le Professeur Elise LAUNAY

Directeur de thèse : Madame le Docteur Myriam BENHAMIDA

Membres du jury :

Madame le Professeur Christèle GRAS-LE GUEN

Madame le Docteur Jocelyne CAILLON

Madame le Docteur Tiphaine BIHOUEE

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TABLE DES MATIERES

TABLE DES ILLUSTRATIONS

INTRODUCTION

Les germes habituellement rencontrés dans les pleuro-pneumopathies infectieuses de l'enfant sont *Streptococcus pneumoniae, Streptococcus pyogenes, et Staphylococcus aureus.* Avant l'intégration du vaccin anti-pneumococcique conjugué dans le calendrier vaccinal, le pneumocoque était le premier germe en cause (1). En 2001 en France, il présentait un pourcentage moyen de sensibilité diminuée à la pénicilline (PSDP) chez l'enfant de moins de 16 ans de 62%, d'après les données du Centre National de Référence des Pneumocoques (CNRP) (2). Dans ce contexte, l'antibiothérapie probabiliste recommandée dans le traitement des pleuro-pneumopathies de l'enfant était une bithérapie par voie intra-veineuse, avec une céphalosporine de 3ème génération (C3G) associée à de la rifampicine ou de la vancomycine (3, 4).

Le vaccin anti-pneumococcique conjugué à 13 valences (PCV13) a été généralisé en 2010 dans le calendrier vaccinal des enfants de moins de 5 ans en France. Ceci a permis une diminution de l'incidence des pneumonies et des pleurésies, ainsi qu'une réduction de la part du pneumocoque dans ces pathologies (5, 6, 7). La généralisation de la vaccination anti-pneumococcique conjuguée a également participé à la diminution de résistance du pneumocoque aux antibiotiques, notamment aux pénicillines et aux macrolides. Ainsi le taux de pneumocoques de sensibilité diminuée à l'amoxicilline dans les infections invasives chez l'enfant de moins de 16 ans en 2014 avait chuté à 3% (8). En parallèle, l'usage de céphalosporines entraîne l'émergence de bactéries à Gram négatif productrices de bêta-lactamases à spectre étendu (BLSE) ou de carbapénémases, qui représentent un problème majeur de santé publique (9).

Dans ce contexte, le protocole de prise en charge des pleuro-pneumopathies de l'enfant au CHU de Nantes a été modifié en 2015, avec une réduction des indications de prescription des C3G. Il préconise en l'absence de tableau sévère et en l'absence de suspicion de *S. aureus*,

l'amoxicilline en antibiothérapie de 1ère intention. En cas de suspicion de *S. aureus* sensible à la méticilline (SASM), il est recommandé de prescrire de l'amoxicilline-acide clavulanique. En présence de signes de gravité, une trithérapie reste indiquée, par amoxicilline-acide clavulanique, clindamycine et clarithromycine. L'indication de prescription de C3G est réservée aux cas d'allergie à l'amoxicilline. Ce protocole limite également la prescription d'examens complémentaires biologiques et radiologiques.

En 2016, le Groupe de Pathologie Infectieuse Pédiatrique (GPIP) a aussi retiré les C3G des antibiothérapies probabilistes des pleuro-pneumopathies de l'enfant (sauf en cas d'allergie aux pénicillines) (10). L'association amoxicilline-acide clavulanique est recommandée en traitement probabiliste, en l'absence de signes de gravité. Dans les tableaux sévères, une trithérapie par amoxicilline-acide clavulanique, vancomycine et clindamycine est proposée. Plusieurs études évaluant les changements épidémiologiques et bactériologiques ont été réalisées suite à la généralisation de la vaccination par le PCV13 (5, 6, 7, 11, 12, 13). Néanmoins, il existe à l'heure actuelle peu de données dans la littérature concernant l'évolution des prescriptions d'antibiotiques « en vie réelle », pour le traitement des pleuro-pneumopathies de l'enfant, après l'introduction du PCV13.

L'objectif principal de cette étude est de déterminer l'impact de la mise en place en 2015 du protocole simplifié d'antibiothérapie dans les pleuro-pneumopathies de l'enfant au CHU de Nantes, avec comme critère de jugement principal l'impact sur la prescription probabiliste de C3G. Les objectifs secondaires sont de comparer les caractéristiques épidémiologiques, cliniques, microbiologiques et thérapeutiques initiales des enfants hospitalisés pour pleuro-pneumopathie au CHU de Nantes avant et après le changement de protocole en 2015, ainsi que de comparer leur évolution et la durée d'hospitalisation. Nous étudierons également l'impact de ce protocole sur la prescription d'examens complémentaires (biologiques et radiologiques) au cours de l'hospitalisation dans cette pathologie.

CONCLUSION

Ce travail montre que la mise en place en 2015 du protocole simplifié d'antibiothérapie dans les pleuro-pneumopathies de l'enfant au CHU de Nantes est associée à une diminution drastique du pourcentage de prescription de C3G (de 89,9% à 12,5%, p<0,001). Cette diminution restait significative après ajustement sur les facteurs de confusion potentiels.

Notre étude retrouve le changement épidémiologique dans les causes bactériennes des pleuro-pneumopathies, qui est à l'origine du protocole. Nous avons observé une diminution de la part du pneumocoque (de 79,2% à 22,2%, p=0,0016) et une augmentation des pourcentages de *S. aureus* (de 5,7% à 33,3 %, p=0,035) et *S. pyogenes* (9,4% à 33,3%, p=0,083). Cette évolution épidémiologique a également été observée dans une récente étude française, conduite entre 2009 et 2017 (6). *S. aureus* et *S. pyogenes* sont potentiellement producteurs de toxines (toxine de Panton et Valentine et exotoxine pyrogène). Ceci peut expliquer l'augmentation significative en période 2 du pourcentage de présence de signes toxiniques, ainsi que la présentation plus sévère des enfants au diagnostic. En effet, le service de prescription initial était plus fréquemment l'unité de réanimation pédiatrique en période 2. Nous avons aussi observé une augmentation du pourcentage de signes de défaillance hémodynamique au diagnostic, bien que non significative. Cette présentation plus sévère retrouvée chez les enfants avec une pleuro-pneumopathie à *S. pyogenes* par rapport à ceux ayant une infection à *S. pneumoniae* avait déjà été décrite dans une étude multicentrique menée par Bellulo *et al* (17).

En parallèle de la diminution notable du pourcentage de prescription de C3G suite à la mise en place du protocole, nous avons observé une augmentation du pourcentage de prescription d'amoxicilline (de 7% à 31,2%, p=0,009) et d'amoxicilline-acide clavulanique (de 0,8% à 43,8%, p < 0,001). Il n'y avait pas de différence significative dans le pourcentage de changement d'antibiothérapie pour échec thérapeutique avant et après mise en place du protocole (18,6% vs 25%, p=0,51). Nous avons néanmoins observé une augmentation des

drainages pleuraux en période 2 (45,7% vs 81,2%, p=0,0074). Ceci est dû à une augmentation des indications pour drainage d'abcès. Or, cette complication est le plus souvent secondaire à une infection à *S. aureus* (18), dont la part augmente en période 2. Il n'y avait par ailleurs pas de différence significative entre les deux périodes concernant le délai d'obtention de l'apyrexie, la durée d'oxygénothérapie, la nécessité d'une ventilation mécanique, la durée d'hospitalisation totale.

Dans notre protocole, nous recommandons l'amoxicilline plutôt que l'amoxicilline-acide clavulanique en traitement de première intention des pleuro-pneumopathies, en l'absence de signes de gravité et d'arguments pour une infection à *S. aureus*. Ceci diffère des recommandations émises par le GPIP en 2016. La question du choix de la monothérapie à prescrire en première intention est bien illustrée par l'étude récente de Leoni *et al* (21). Ils ont évalué, avec la méthode DELPHI, les pratiques d'experts concernant la prise en charge des pleuro-pneumopathies en France en 2018. Ils montrent l'absence de consensus quant à l'antibiotique à utiliser, l'amoxicilline ou l'amoxicilline-acide clavulanique. Notre choix est lié au fait que l'amoxicilline-acide clavulanique participe à la diffusion des bactéries à Gram négatif BLSE. *S. pneumoniae* et *S. pyogenes* restent actuellement sensibles à l'amoxicilline. De plus, les échecs d'antibiothérapie retrouvés en seconde période ne sont pas liés à un *S. aureus* traité par amoxicilline. Ainsi, les indications de traitement par amoxicilline semblent bien définies dans notre protocole, et permettent d'éviter l'utilisation de l'amoxicilline-acide clavulanique dans 30% des cas. Par ailleurs, alors que le GPIP recommande, en présence de signes de gravité, une trithérapie par amoxicilline-acide clavulanique, clindamycine et vancomycine dans le but de couvrir le *S. aureus* résistant à la méticilline (SARM), notre protocole propose une trithérapie par amoxicilline-acide clavulanique, clindamycine et clarithromycine pour couvrir *Mycoplasma pneumoniae*. Le linézolide n'est ajouté qu'en cas de suspicion de SARM. Or dans cette étude, un SARM a été documenté en période 2 (il s'agit d'un des 4 cas de changement d'antibiothérapie pour échec thérapeutique). En parallèle, aucun

M. pneumoniae n'a été retrouvé. D'autres études, conduites récemment en France et en Allemagne, trouvaient également un taux de SARM plus important que celui de *M. pneumoniae* dans les pleuro-pneumopathies (6, 12). Ceci pose la question de la pertinence du choix d'un macrolide, plutôt que de la vancomycine ou du linézolide, en présence de signes de gravité dans notre protocole, bien que le SARM soit un germe relativement rare dans notre région.

Il n'y avait pas de différence significative entre les deux périodes concernant la durée moyenne d'antibiothérapie (environ 4 semaines). Néanmoins, la durée d'antibiothérapie intraveineuse était significativement diminuée en période 2. Cela peut être expliqué en partie par la diminution de prescription d'examens complémentaires biologiques après la mise en place du protocole, la décision du relais de l'antibiotique par voie orale était plus basée sur l'amélioration clinique que sur les marqueurs biologiques.

Cette étude comporte certaines limites. Tout d'abord le caractère rétrospectif a conduit à des données manquantes. De plus, cette étude est monocentrique, avec un faible effectif d'enfants en période 2. Ceci est probablement lié en partie à la diminution d'incidence des pleuro-pneumopathies suite à la généralisation du PCV13. Néanmoins, notre population est comparable à celle décrite dans de précédentes études d'enfants hospitalisés pour pleuro-pneumopathies. L'âge médian est similaire à celui décrit dans l'étude canadienne de Haji *et al* (13) et l'étude française de Madhi *et al* (6), pour des périodes comparables. Par ailleurs, une ponction pleurale a été effectué au diagnostic dans un peu moins de la moitié des cas, avec un taux de confirmation microbiologique de l'infection de 42,8%, ce qui est également cohérent avec les résultats rapportés dans les études de Madhi *et al* (6) et Erlichman *et al* (19).

Comme précédemment démontré, la mise en place de recommandations locales est un moyen efficace pour modifier et améliorer les pratiques (26, 27). Dans le contexte actuel de résistance des bactéries aux antibiotiques, de telles interventions permettant de diminuer la prescription d'antibiotiques à large spectre, en évaluant les résultats obtenus, sont nécessaires.

Au total, la mise en place en 2015 du protocole simplifié d'antibiothérapie dans les pleuro-pneumopathies de l'enfant au CHU de Nantes est associée à une diminution significative de la prescription de C3G, sans augmentation perceptible de la morbidité. L'augmentation relative de *S. aureus* et de *S. pyogenes* impose leur prise en compte lors du choix de l'antibiothérapie probabiliste, notamment en cas de syndrome toxinique. Dans notre étude, la prescription en probabiliste d'amoxicilline en l'absence de signe de gravité ou d'argument pour une infection à *S. aureus* n'a pas conduit à des échecs thérapeutiques. La question de couvrir ou non le mycoplasme et le SARM dans les tableaux sévères reste d'actualité, et nécessite des études de plus forte puissance pour y répondre.

ARTICLE AU FORMAT PEDIATRIC PULMONOLOGY

TITLE

Impact of the implementation in 2015 of the guidelines for antibiotic therapy in community-acquired parapneumonic effusion / pleural empyema in children on the prescription of third-generation cephalosporins at the Nantes University Hospital.

KEY WORDS

Children, guidelines, parapneumonic effusion, pleural empyema, *S. pneumoniae*, third generation cephalosporins.

ABSTRACT

Introduction: The implementation of the 13-valent pneumococcal conjugate vaccine in 2010 has led to a reduction in the proportion of penicillin non-susceptible *S. pneumoniae*. In this context, the guidelines for the management of community-acquired parapneumonic effusion and pleural empyema (PPE/PE) at the Nantes University Hospital were changed in 2015, in order to avoid the prescription of third generation cephalosporins (3GC) and prefer a narrow-spectrum antibiotic as amoxicillin.

Objective: To evaluate the impact of the guidelines implemented in 2015, for the management of community-acquired PPE/PE in children.

Methods: We conducted a monocentric, retrospective study, to compare two periods, before (2003-2014) and after (2016-2018) the implementation of the guidelines. Children younger than 18 years of age hospitalized for community-acquired PPE/PE were included. The main outcome was the impact of the guidelines on the empiric prescription of 3GC. As balancing measure, we evaluated the outcome of children during hospitalization.

Results: There were 129 children included in 2003-2014 and 16 children in 2016-2018. After the implementation of the guidelines, whereas the empiric prescription of 3GC was reduced from 89.9% to 12.5% ($p < 0.001$), those of amoxicillin and amoxicillin-clavulanate increased respectively from 7% to 31.2% ($p=0.009$) and from 0.8% to 43.8% ($p < 0.001$). In period 2, there were no significant differences in rates of change of antibiotic therapy for treatment failure (18.6% vs 25%, $p=0.51$), as in the hospital length of stay (13 days vs 11.5 days, $p=0.21$). Proportions of *Staphylococcus aureus* and *Streptococcus pyogenes* increased significantly between the two periods, respectively from 5.7% to 33.3% ($p=0.035$), and from 9.4% to 33.3%, ($p=0.083$).

Conclusion: The implementation of the guidelines for the management of PPE/PE in 2015 was associated with a significant decrease in the prescription of 3GC, without discernible increase in the morbidity.

ABBREVIATIONS

3CG	Third Generation Cephalosporins
CBC	Complete Blood Count
CRP	C-Reactive Protein
CXR	Chest X-ray
ESLB	Extended-Spectrum β-Lactamase
GAS	Group A Streptococcus
GPIP	French Group of Pediatric Infectious Diseases
ICU	Intensive Care Unit
IV	Intravenous
LOS	Length of Stay
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin-Resistant *S.aureus*
MSSA	Methicillin-Susceptible *S.aureus*
NRCP	National Reference Centre for Pneumococci
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NUH	Nantes University Hospital
PCT	Procalcitonin
PCV13	13-Valent Pneumococcal Conjugate Vaccine
PE	Pleural Empyema
PMSI	Medical Program of Information System
PPE	Parapneumonic Effusion

1. INTRODUCTION

The most common bacterial causes of parapneumonic effusion and pleural empyema (PPE/PE) in children are *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A Streptococcus [GAS]) and *Staphylococcus aureus*. Before the implementation of pneumococcal conjugate vaccines (PCVs), *S. pneumoniae* was the leading cause of PPE/PE (1). In 2001 in France, the mean percentage of penicillin non-susceptible *S. pneumoniae* in children younger than 16 years of age was 62%, based on the data from the National Reference Centre for Pneumococci (NRCP) (2). In this context, the empiric antibiotic therapy recommended for the treatment of PPE/PE was an intravenous bitherapy, with a third generation cephalosporin (3GC) associated with rifampicin or vancomycin (3,4).

In 2010, the French authorities recommended routine vaccination with 13-valent pneumococcal conjugate vaccine (PCV13). This implementation has led to a reduction in the overall incidence of pneumonia and empyema, as well as a reduction in the proportion of *S. pneumoniae* in these diseases (5, 6, 7). This has also contributed to the reduction of its resistance to antibiotics, notably to penicillins and macrolides. Thus, the rate of amoxicillin non-susceptible *S. pneumoniae* in invasive infections in children younger than 16 years of age in 2014 dropped to 3% (8). Furthermore, antibiotic resistance is a major problem, particularly with the emergence of extended-spectrum β-lactamase (ESBL)- producing gram-negative bacilli. 3GC has been clearly identified as a risk factor for ESBL carriage or infection (9).

In this context, guidelines for the management of community-acquired PPE/PE at the Nantes University Hospital (NUH) were changed in 2015, with a reduction in the indications of 3GC prescriptions. In the absence of signs of severity or suspected *S. aureus* infection, the empiric antibiotic therapy advocated is amoxicillin. If methicillin-susceptible *S. aureus* (MSSA) is suspected, the prescription of amoxicillin-clavulanate is recommended. In the presence of signs of severity, a tritherapy is nevertheless indicated, with amoxicillin-clavulanate, clindamycin and

clarithromycin. The prescription of 3GC is limited to cases with allergy to amoxicillin. These guidelines also limit the prescription of biological and radiological tests.

In 2016, the French Group of Pediatric Infectious Diseases (GPIP) published guidelines for the treatment of pleural empyema in children, and the use of 3GC in first-line treatment is also no more warranted (except in case of allergy to penicillins). The first empiric antibiotic treatment recommended in the absence of signs of severity is amoxicillin-clavulanate. In presence of these signs, a tritherapy is also recommended, with amoxicillin-clavulanate, vancomycin and clindamycin (10).

Several studies assessing the epidemiological and bacteriological changes since the implementation of the PCV13 were conducted (5, 6, 7, 11, 12, 13). However, there is little data in the literature concerning the evolution in antibiotic prescriptions for children with PPE/PE, after the PCV13.

The aim of this study was to evaluate the impact of the implementation in 2015 of the guidelines for the antibiotic therapy in community-acquired PPE/PE in children, at the NUH. We hypothesized that the empiric prescription of 3GC would be reduced, hence the main outcome was the proportion of patients hospitalized receiving this treatment, before and after the implementation of the guidelines. As secondary outcomes, we also aimed to compare the epidemiological, clinical and bacteriological changes of children with PPE/PE at diagnosis, as well as their outcome during the hospitalization. In addition, we assessed the impact on the prescription of bacteriological and radiological tests.

2. METHODS

2.1 Description of the guidelines

In 2015, pediatric pneumologists and pediatric infectious disease specialists worked to provide new guidelines for the antibiotic therapy in community-acquired PPE/PE in children hospitalized in NUH. In the absence of signs of severity or suspected *S. aureus* infection, the first-line antibiotic therapy was a monotherapy with amoxicillin, 100 mg/kg/day per os in small well tolerate effusion, or 150 to 200mg/kg/day intravenous (IV) in case of more important pleural effusion that may require pleural puncture. If *S. aureus* infection was suspected, the prescription of amoxicillin-clavulanate 150 to 200 mg/kg/day IV was recommended, with clindamycin 30 to 40 mg/kg/day in the presence of toxin-related signs. In the presence of signs of severity, a tritherapy was indicated, with amoxicillin-clavulanate, clindamycin and clarithromycin 15 mg/kg/day. Intravenous antibiotic therapy was continued until clinical improvement, and total duration recommended was between 2 and 6 weeks. Tests usually performed for the diagnosis and the monitoring of pleural empyema were inflammatory blood tests, chest X-ray (CXR), and pleural ultrasonography. Computerized tomography (CT) scan may be performed in particular cases, especially in case of first-line antibiotic therapy failure. In the guidelines, the control of inflammatory blood tests was not recommended if the clinical course was favorable. Moreover, one CXR every 7-10 days was sufficient in the absence of clinical degradation. The guidelines were integrated into the NUH guidelines book, and was readily accessible online via the hospital's intranet website.

2.2 Setting and study design

We conducted a retrospective, monocentric study, in the pediatric wards of the NUH. We compared two periods, before and after the implementation of the guidelines in 2015. The first period was from January 2003 to December 2014 (Period 1), and the second period from

January 2016 to December 2018 (Period 2). We determined 2015 as a transition year. The project was approved by the institutional review board at the NUH (Groupe Nantais d'Ethique dans le Domaine de la Santé). French legislation stipulates that informed consent is not required, and local retrospective data may be used for an epidemiological study. We followed SQUIRE guidelines to report this study.

2.3 Study population and data collection

Eligible subjects were infants younger than 18 years of age, hospitalized for PPE, PE or lung abscess with pleural effusion. PPE and PE were defined by the association of fever and CXR showing pleural effusion. Using the NUH Medical Program of Information System (PMSI), we screened for all patients with the diagnosis of PPE/PE, defined by the group of codes 'pyothorax' and 'lung abscess' of the International Classification of Disease 10 (J85.0, J85.1, J85.2, J86.0, J86.9), and who were hospitalized in pediatric units of the NUH during the inclusion period. Exclusion criteria included children older than 18 years of age, aspecific pleural effusion post-operative (i.e after cardiac surgery), and obvious mistakes in the PMSI such as the absence of any clinical or radiological signs of pleural empyema in their medical files. We also excluded newborn hospitalized in neonatal units and children with particular comorbidities (for example cystic fibrosis, hematological malignancies …), who did not fit into the protocol for community-acquired PPE/PE.

Epidemiological, clinical, and biological characteristics at diagnosis were collected. The vaccination was considered up-to-date according to the current vaccination schedule the year of the diagnosis. Toxin-related signs were rash and diarrhea. Signs of hemodynamic failure were defined according to 2015 European Resuscitation Council Guidelines (14). Minimal inhibitory concentration (MIC) breakpoints for *S. pneumoniae* isolates were determined according to Eucast methods, with breakpoints for penicillin G as follows: susceptible, MIC $\leq$ 0.06 µg/mL, and fully resistant, MIC > 2 µg/mL, and for amoxicillin as follow:

susceptible, MIC ≤ 2 μg/mL and fully resistant, MIC > 2 μg/mL (15, 16).

Data were collected by the retrospective review of medical files, tabulated using Excel (Microsoft, Redmond, Washington, USA).

2.4 Assessment of the impact of the guidelines

Our primary outcome was the proportion of 3GC prescribed prior the implementation of the guidelines compared to that after.

As secondary outcomes, we compared epidemiological, clinical, and biological characteristics of the patients before and after the implementation of the guidelines. We also compared bacterial causes identified, with the methods of identification, between the two periods. As a balancing measure, we assessed the change of the empiric antibiotics for treatment failure. Moreover, to evaluate whether the implementation of the protocol affected the outcome of children during the hospitalization, we assessed the time to obtain apyrexia, the duration and the level of oxygen supplementation, the duration and the type of intravenous infusion, the necessity of chest tube placement or other surgical procedure, the length of stay (LOS) in hospital, hospitalization in intensive care unit (ICU) or resuscitation unit, and the rate of death. In addition, we compared the duration of antibiotic treatment between the two periods. Finally, we assessed the impact of the guidelines on the number of prescriptions of biological tests and CXR.

2.5 Statistical analysis

Continuous variables were expressed as medians and IQRs if their distribution was abnormal, and as means and SD if the distribution was normal. Categorial variables were expressed as percentages. For the univariate analyses (comparing period 1 to period 2), we used either the chi-squared or Fisher's exact test to compare the categorial variables, and either Student's *t*-test or the Mann-Whitney test to compare the continuous variables. We compared the proportion of

3GC prescribed between the two periods with the Fisher's exact test. In order to take into account the variability between groups (before and after protocol) for variables potentially associated with 3GC prescription, we adjusted the comparison of confounding factors using logistic regression. A *p*-value of < 0.05 was considered significant.

Statistical analyses were performed using R software, version 3.6.1 and Stata, v15.

3. RESULTS

3.1 Characteristics of the study population

During the study period, 170 patients with the diagnosis of PPE/PE hospitalized at the NUH were eligible for the study (Figure 1). 20 were excluded, hence 150 patients were included in the study: 129 children in the period 1, before de implementation of the protocol; 5 in the transition period; and 16 in the period 2, after the implementation of the protocol.

The median age was 46 months in period 1 and 24.5 months in period 2 (p=0.11). In period 2, children were significantly more vaccinated with a PCV (84.6%) than in period 1 (32.4%) (p=0.001), and had received significantly less non-steroidal anti-inflammatory drugs (NSAIDs) before admission (6.2% vs 38%, p=0.012). There was no difference in signs of clinical gravity (oxygen saturation <92%, hypercapnia, hemoptysis, hemodynamic failure) at diagnosis between the two periods, except for toxin-related signs, which were more present in period 2 (25% vs 4.7%, p=0.014). Concerning biology data, C-reactive protein (CRP) and procalcitonin (PCT) were significantly lower in period 2 (Table 1).

3.2 Microbiological diagnosis

A pleural puncture at diagnosis was performed for 60/129 children (46.5%) in period 1 and for 7/16 children (43.8%) in period 2 (p=0.835). A bacterial pathogen was identified in 62/145 cases (42.8%) (Table 2). On one hand, the frequency of *S. pneumoniae* decreased significantly between the two periods, from 79.2% to 22.2% (p=0.0016). No Data on penicillin G susceptibility were available for 15 *S. pneumoniae* in period 1 : 10/15 (66.7%) were penicillin susceptible, 3/15 (20%) were intermediate resistant and 2/15 (13.3%) were fully penicillin-resistant. No data on penicillin G susceptibility was available for strains in period 2. Concerning susceptibility to amoxicillin, data were available for 19 *S. pneumoniae* in period 1, and all strains were amoxicillin susceptible. For 4/19 (21%), MIC was > 0.5 µg/mL. In period 2, data

was available for one strain, which was amoxicillin susceptible, with a MIC < 0.5 µg/mL. On the other hand, the frequency of *S. aureus* increased significantly between the two period, from 5.7% to 33.3% (p=0.035). There were 2 methicillin-resistant *S. aureus* (MRSA) strains in period 1 and 1 in period 2. There was also an increase in the percentage of GAS (9.4% in period 1 vs 33.3% in period 2, p=0.083).

3.3 Changes in the empiric antibiotic treatment

There were no significant differences for patients 'characteristics between the group of children with a 3CG as empiric antibiotic treatment and the group with another empiric antibiotic (age, previous medical history, clinical severity criteria, initial prescriber or initial prescription unit), except for the PCV, with more children fully vaccinated in the group 'other antibiotics' (p=0.023) and in terms of previous treatment by NSAIDs, more frequent in the group treated with 3CG (p < 0.001) (Table 1 supp).

Empiric antibiotic treatment differed significantly between the two periods (Table 3). The percentage of 3CG prescriptions decreased dramatically, from 89.9% before the implementation of the protocol to 12.5% after (p < 0.001). At the same time, the percentage of amoxicillin and amoxicillin-clavulanate prescriptions increased significantly, respectively from 7% to 31.2% (p=0.009) and from 0.8% to 43.8% (p < 0.001). The prescription of other antibiotics (fosfomycin, rifampicin, vancomycin) also decreased, except for clindamycin, which increased. In addition, the prescription of an association of antibiotics decreased, with more monotherapy in period 2 (68.8% vs 13.3% in period 1, p < 0.001). Initial prescription unit was significantly more often the resuscitation unit in period 2 (p=0.048).

After adjustment for potential confounding factors (age, toxin-related signs, and hospitalization in resuscitation unit), period 2 remained significantly associated a lower risk of prescription of 3GC (aOR= 0.09 [95% CI:0.02-0.4]; p=0.001), and an increased risk of toxin-related signs (aOR = 7.7 [1.5-39]; p=0.014) (Table 4).

3.4 Outcome of children

As a balancing measure, we assessed the change of the empiric antibiotic therapy for treatment failure. In the period 1, treatment failure occurred in 24/129 cases (18.6%), while it occurred in 4/16 cases (25%) in period 2 (p=0.51). Table 2 supplement summarized the causes of change in antibiotic prescription in period 2.

No significant differences between the two periods were observed in duration of fever, oxygen use, mechanical ventilation, intravenous infusion duration and hospital LOS after the diagnosis (Table 5). There were significantly more chest tube placements in period 2 (81.2%), than in period 1 (45.7%) (p=0.0074), with an increased indication for abscess drainage. More children were hospitalized in ICU (5.4% vs 68.8%, p<0.001), but there were no differences in hospitalizations in resuscitation unit (38% vs 43.8%, p=0.66). All infants survived, and more than two third were followed by a pediatric pneumologist or pediatric infectious disease specialist after discharge from the hospital.

The mean antibiotic treatment total duration in period 1 and 2 was 33 (+/- 11.9) days and 33.8 (+/-14.2) days respectively (p=0.83). The median duration of intravenous treatment was 11 days (range 7-15) in period 1 and 6 days (range 4 -9.8) in period 2 (p=0.015).

3.5 Additional tests

In period 2, we noticed a significant reduction in the prescription of inflammatory blood tests (CBC, CRP, PCT). However, there was no decrease in the number of CXR (Table 6). 24/129 (18.6%) children had a CT scan in period 1, and 4/16 (25%) in period 2 (p=0.513). Concerning pleural ultrasonography, the exam was performed for 99/129 (76.7%) children in period 1 and for 12/16 (75%) children in period 2 (p=1.0).

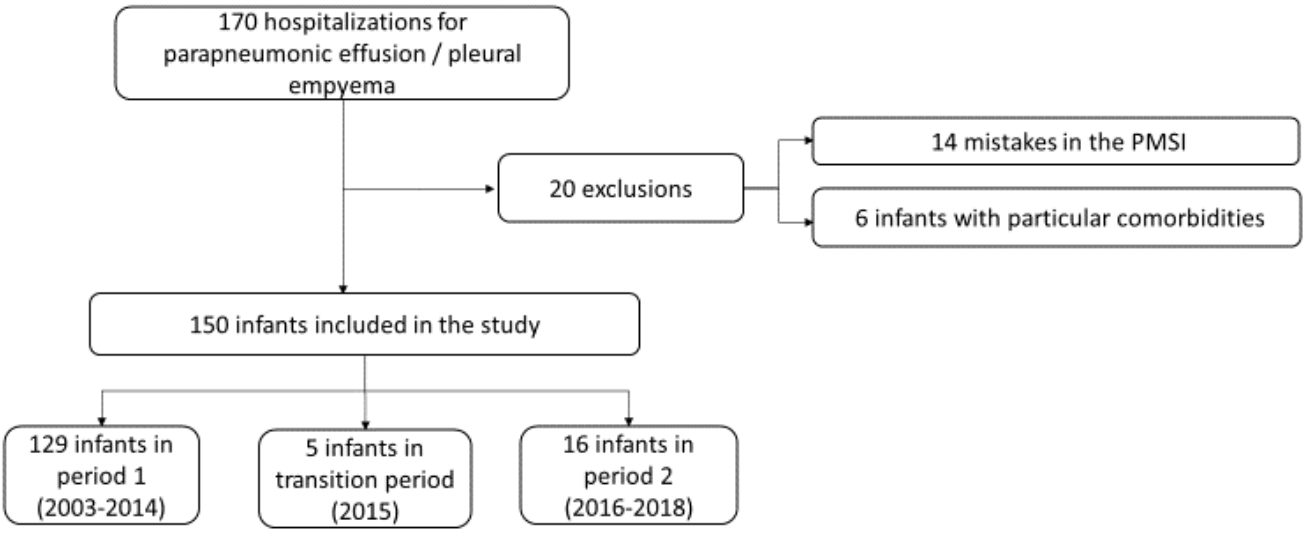

Figure 1 - Flow chart of the infants included in the study

PMSI : Medical Program of Information System

Table 1 - Demographic, clinical and biological characteristics of the children at diagnosis, according to the period, univariate analysis

Variables	Period 1 (2003-2014) (N=129) n/N	Period 2 (2016-2018) (N=16) n/N	*P*-value
Age, months, median (IQR)	46 (28-80)	24.5 (8.5-108.5)	0.11
Gender, male, n (%)	73/129 (56.6)	6/16 (37.5)	0.15
Weight, kg, median (IQR)	17 (12-21.5)	11.7 (7.7-31.5)	0.11
Previous medical history, n (%)	33/129 (25.6)	7/129 (43.8)	0.14
Underlying lung disease[a], n (%)	20/129 (15.5)	4/129 (25)	0.31
Preterm birth, n (%)	3/129 (2.3)	0/16	1
History of severe pulmonary infection, n (%)	1/129 (0.8)	0/16	1
Regular medical treatment, n (%)	19/129 (14.7)	5/16 (31.2)	0.15
Up-to-date vaccination, n (%)	37/61 (60.7)	8/12 (66.7)	0.76
Fully vaccinated with a PCV, n (%)	23/71 (32.4)	11/13 (84.6)	**0.001**
Drug allergy, n (%)	3/129 (2.3)	0/16	1
Previous treatment by NSAIDs, n (%)	49/129 (38)	1/16 (6.2)	**0.012**
Previous treatment by corticosteroid, n (%)	9/129 (7.0)	2/16 (12.5)	0.35
Previous antibiotic treatment, n (%)	82/129 (63.6)	10/16 (62.5)	0.93
Oxygen saturation (%), median (IQR)	96 (93-97)	95 (92-96)	0.2
Oxygen saturation < 92%, n (%)	18/114 (15.8)	3/15 (20)	0.71
O2 max at diagnosis, L/min, median (IQR)	1.0 (0.5-2.0)	1.0 (1.0-1.0)	0.73
FiO2 max, %, median (IQR)	47.5 (31.5-100)	40 (40.0-40.0)	1
Hypercapnia, n (%)	5/119 (4.2)	1/15 (6.7)	0.52
Hemodynamic failure, n (%)	8/129 (6.2)	2/16 (12.5)	0.3
Toxin-related signs, n (%)	6/129 (4.7)	4/16 (25)	**0.014**
Hemoptysis, n (%)	1/129 (0.8)	1/16 (6.2)	0.21
Biology at diagnosis			
Leucocytes, /mm³, median (IQR)	19000 (12000-260000)	15000 (10300-23275)	0.56
PNN, /mm³, median (IQR)	14200 (8000-20000)	11800 (6650-17925)	0.55
CRP, mg/ml, median (IQR)	263 (140-333)	138 (93-171)	**0.016**
PCT, mg/ml, median (IQR)	8.3 (1.9-18.3)	2.27 (0.28-5.1)	**0.022**
Hospital at diagnosis, NUH, n (%)	96/129 (74.4)	12/16 (75)	1

[a]23 asthma, 1 tuberculosis disease

IQR, interquartile range; PCV, pneumococcal conjugate vaccine; O2, oxygen therapy; FiO2, fraction of inspired oxygen; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; NUH, Nantes University Hospital; CBC, complete blood count; CRP, C-reactive protein; PCT, procalcitonin.

Table 2 - Bacterial causes identified in children hospitalized for PPE/PE, according to the period

Bacterial cause	Total (N=62/145)	Period 1 (2003-2014) (N= 53) n/N	Period 2 (2016-2018) (N= 9) n/N	*P*-Value
Streptococcus pneumoniae, n (%)	44/62 (71)	42/53 (79.2)	2/9 (22.2)	**0.0016**
Positive pleural culture	12	12	0	
Positive pleural Ag	19	18	1	
Positive pleural PCR	7	7	0	
Positive blood culture	13	12	1	
Positive urinary Ag	4	4	0	
Penicillin G resistant germ[a], n (%)		2/15 (13.3)	–	
GAS, n (%)	8/62 (12.9)	5/53 (9.4)	3/9 (33.3)	0.083
Positive pleural culture	8	5	3	
Positive pleural PCR		0	0	
Positive blood culture		0	0	
Resistant germ, n (%)		0/5	0/3	
Staphylococcus aureus, n (%)	6/62 (9.7)	3/53 (5.7)	3/9 (33.3)	**0.035**
Positive pleural culture	4	1	3	
Positive pleural PCR		0	0	
Positive blood culture	4	2	2	
MRSA, n (%)		2/3 (66.7)	1/3 (33.3)	1
Toxin secretion, n (%)		1/3[b]	0/3	
Others[c], n (%)	4/62 (6.5)	3/53 (5.7)	1/9 (11.1)	0.48

[a] Data on susceptibility were available for 15 strains in period 1, no data in period 2

[b] Methicillin-resistant producing Panton and Valentine toxin (PVL+) *S. aureus*

[c] Other germs identified: 1 *Mycoplasma pneumoniae*, 2 *Streptococcus milleri* (1 in period 2), 1 *fusobacterium*

GAS, Group A Streptococcus; PCR, Polymerase Chain Reaction; MRSA, Methicillin-Resistant *S. aureus*

Table 3 - Description of the modalities of empiric antibiotic prescription, according to the period

Variables	Period 1 (2003-2014) (N=129) n/N	Period 2 (2016-2018) (N=16) n/N	*P*-Value
Empiric antibiotic prescription			
3GC, n (%)	116/129 (89.9)	2/16 (12.5)	**< 0.001**
Amoxicillin, n (%)	9/129 (7)	5/16 (31.2)	**0.009**
Amoxicillin-Clavulanate, n (%)	1/129 (0.8)	7/16 (43.8)	**< 0.001**
Vancomycin, n (%)	35/129 (27.1)	1/16 (6.3)	0.12
Rifampicin, n (%)	43/129 (33.3)	0/16	**0.0031**
Fosfomycin, n (%)	25/129 (19.4)	0/16	0.075
Clindamycin, n (%)	0/129	3/16 (18.8)	**0.0011**
Macrolide, n (%)	12/129 (9.3)	0/16	0.36
Others, n (%)	11/129 (8.5)	3/16 (18.8)	0.19
Posology, mg/kg/day, median (IQR)			
3GC			
Cefotaxime	200 (150-200)	175 (162.5-187.5)	0.68
Ceftriaxone	50 (50-51.3)	0	–
Amoxicillin	150 (122.5-150)	150 (150-200)	0.093
Amoxicillin-Clavulanate	150	150 (145-155)	0.85
Amoxicilline	150	150 (145-155)	1
Clavulanate	15	16 (15-18)	1
Mode			
IV, n (%)	104/129 (80.6)	14/16 (87.5)	0.74
Oral, n (%)	25/129 (19.4)	2/16 (12.5)	0.74
Antibiotic association			
Monotherapy, n (%)	21/129 (16.3)	11/16 (68.8)	**< 0.001**
Bitherapy, n (%)	93/129 (72.1)	5/16 (31.2)	**< 0.001**
Tritherapy, n (%)	15/129 (11.6)	0/16	0.38
Initial Prescriber			
Pediatrician, n (%)	112/129 (86.8)	10/16 (62.5)	**0.023**
Pediatric critical care specialist, n (%)	12/129 (9.3)	5/16 (31.2)	**0.024**
Surgeon, n (%)	5/129 (3.9)	0/16	1
Initial prescription unit			
Emergency department, n (%)	97/129 (51.9)	9/16 (56.2)	0.745
Pediatric ward, n (%)	40/129 (31)	2/16 (12.5)	0.153
Resuscitation unit, n (%)	15/129 (11.6)	5/16 (31.2)	**0.048**
ICU, n (%)	1/129 (0.8)	0/16	1
Surgery department, n (%)	6/129 (4.7)	0/16	1

3GC, third generation cephalosporins; IQR, interquartile range; IV, intravenous; ICU, intensive care unit

Table 4 - Factors independently associated with the period 2 (after the implementation of the guidelines), multivariate analysis

	aOR (95% CI)	*P*-Value
3CG	0.09 (0.02-0.4)	**0.001**
Age[a]	1.0 (0.9-1.0)	0.80
Presence of toxin-related signs	7.7 (1.5-39)	**0.014**
Hospitalization in resuscitation unit	2.1 (0.6-7.1)	0.22

3CG, third generation cephalosporins; aOR, adjusted Odd Ratio; CI, Confidence Interval
[a]entered as continuous variable

Table 5 - Outcome of children hospitalized, according to the period

Variables	Period 1 (2003-2014) (N=129) n/N	Period 2 (2016-2018) (N=16) n/N	*P*-Value
Time to obtain apyrexia, days, median (IQR)	7 (3-11)	4.5 (1.8-6.3)	0.19
Oxygen use, n (%)	96/129 (74.4)	13/16 (81.2)	0.76
O2 max, L/min, median (IQR)	1 (1-2)	1 (1-1.8)	0.93
FiO2[a] max, %, median (IQR)	50 (40-60)	35 (30-40)	**0.013**
Non-invasive ventilation, n (%)	4/129 (3.1)	0/16	1
Mechanical ventilation, n (%)	8/129 (6.2)	1/16 (6.2)	1
Oxygen duration, days, median (IQR)	8 (4-11)	6 (2-7)	0.055
Nasogastric fluid replacement, n (%)	15/129 (11.6)	5/16 (31.2)	**0.048**
Nasogastric fluid duration, days, mean (+/-SD)	15.5 +/- 8.4	6.4 +/- 6.7	**0.037**
Intravenous infusion, n (%)	125/129 (96.9)	16/16 (100)	1
Intravenous infusion duration, days, median (IQR)	11 (7-15)	8 (5.8-11.3)	0.092
Parenteral nutrition, n (%)	47/129 (36.4)	2/16 (12.5)	0.056
Parenteral nutrition duration, days, median (IQR)	9 (7-12.5)	5.5 (3.75-7.25)	0.275
Chest tube placement, n (%)	59/129 (45.7)	13/16 (81.2)	**0.0074**
For poor clinical tolerance, n (%)	32/59 (54.2)	7/13 (53.8)	0.98
For volume of effusion, n (%)	43/59 (72.9)	6/13 (46.2)	0.098
For prolonged evolution, n (%)	7/59 (11.9)	1/13 (7.7)	1
For abscess associated, n (%)	2/59 (3.4)	4/13 (30.8)	**0.0083**
For other cause, n (%)	5/59 (8.5)	0/13	0.58
Duration of chest tube, days, median (IQR)	6 (4-8)	5 (4-7)	0.29
Use of fibrinolysis, n (%)	0/129	0/16	1
Thoracotomy, n (%)	3/129 (2.3)	0/16	1
Video-assisted thoracoscopic surgery, n (%)	11/129 (8.5)	4/16 (25)	0.064
ICU or resuscitation unit hospitalization, n (%)	53/129 (41.1)	14/16 (87.5)	**< 0.001**
ICU, n (%)	7/129 (5.4)	11/16 (68.8)	**< 0.001**
Resuscitation unit, n (%)	49/129 (38)	7/16 (43.8)	0.66
LOS in ICU, mean (+/- SD)	9.6 +/- 3.3	6.7 +/- 3.5	0.091
LOS in Resuscitation service, median (IQR)	3 (2-7)	4 (2-5)	0.99
Length of stay (LOS) in hospital, days, median (IQR)	13 (9-17)	11.5 (7-13)	0.21
Pneumologist or infectious disease pediatrician follow-up, n (%)	81/120 (67.5)	14/16 (87.5)	0.15

IQR, Interquartile range; LOS, length of stay; ICU, intensive care unit; O2, oxygen therapy;
[a] 21 patients in period 1, 6 patients in period 2

Table 6 - Additional tests, according to the period

Variables (Number of each test per child)	Period 1 (2003-2014)[a]	Period 2 (2016-2018) [b]	*P*-value
CBC, median (IQR)	3 (2.0-5.0)	2 (2.0-3.0)	**0.026**
CRP, median (IQR)	3 (2.0-5.0)	2 (1-2.3)	**0.011**
PCT, median (IQR)	1 (0-2.0)	1 (0-1.0)	**0.048**
Blood culture, median (IQR)	1 (1.0-2.0)	1 (1-1.25)	0.23
CXR, median (IQR)	4 (2.0-6.0)	5 (3.5-7.0)	0.28

CBC, complete blood count; CRP, C-reactive protein; PCT, procalcitonin, CXR, chest X-ray
[a]In period 1, CBC was done for 124 children, CRP for 124, PCT for 60, blood culture for 116, CXR for 129
[b]In period 2, CBC was done for 15 children, CRP for 16, PCT for 12, blood culture for 14, CXR for 16

4. DISCUSSION

In this retrospective study on children hospitalized for community-acquired PPE/PE, we observed a drastic decrease in the prescription of 3GC after implementation of guidelines (from 89.9% to 12.5%, p<0.001). This decrease persists after adjustment for potential confounders.

Our findings confirmed also the epidemiological change in the bacterial etiology of PPE/PE, that was at the origin of the guidelines implementation. Indeed, the frequency of *S. pneumoniae* significantly decreased from 79.2% before 2015 to 22.2% after. And the proportion of *S. aureus* and GAS both increased to reach 33.3% in period 2. In comparison, Madhi *et al*, in their study conducted between 2009 to 2017, found a decrease in the frequency of *S. pneumoniae* infections from 79.1% to 36.4% between the pre-PCV13 era and 5 years after its implementation, and an increase in the frequency of GAS and *S. aureus* infections, respectively from 6.4% to 45.5% and from 12.7% to 18.2% (6). Concerning *S. pneumoniae*, our results concerning the antibiotic susceptibility of the stains before 2015 were similar to those described in the French study of Angoulvant *et al* (11). After 2015, data on antibiotic susceptibility was only available for one strain of *S. pneumoniae*. Nevertheless, the NRCP described in 2017 a percentage of resistance of *S. pneumoniae* to amoxicillin still less than 2% (16). Of note we must point out the increase since 2014 in the rate of strains penicillin intermediate or fully penicillin resistant, based on the data from the NRCP. *S. aureus* and GAS can produce toxins (Panton and Valentine toxin and pyogenic exotoxin respectively). The increasing proportion of these germs probably explains the significant increase in toxin-related signs observed between the two periods in our study, as well as the increase of the severity of the patients at the admission. Indeed, the initial prescription unit was more frequently the resuscitation unit in period 2. Moreover, there was a trend to a higher proportion of hemodynamic failure in period 2. And the 2 cases reported in this period were linked with GAS infections. Those observations are similar to those of a recent multicentre French study conducted by Bellulo *et al*. They showed that children with GAS

empyema were more severe than children with *S. pneumoniae* empyema, with more frequently rashes and signs of circulatory failure at admission, and more transfer to the ICU (17). Finally, previous studies have shown that *S. aureus* and GAS PE often occurred in younger children compared with *S. pneumoniae* PE (7, 17). This could explain the decreasing trend in the median age that we observed in period 2.

Concerning PPE/PE management, the decrease in the percentage of 3GC prescriptions was associated with an increase in amoxicillin and amoxicillin-clavulanate prescriptions in period 2. There were no significant differences in rates of change of the empiric antibiotic therapy for treatment failure between the two periods. However, we observed significantly more chest tube placements in period 2. This was due to increased indications for abscess drainage, this complication being related most often with *S. aureus* infections (18). For comparison, the rate of 45.7% of chest tube placements before 2015 is concordant with other studies (1, 13), however there is no recent data on this rate after 2016. We noticed an increase in hospitalizations in ICU in period 2. Nevertheless, there were no significant differences in rates of hospitalizations in resuscitation unit between the two periods. The ICU opened in 2012, and probably children who were before 2012 hospitalized in surgery unit were after 2012 hospitalized in ICU. There were no differences in the LOS in hospital, respectively 13 and 11.5 days in period 1 and 2. Those lengths are similar with those of previous studies (19, 20).

In 2016, the GPIP published guidelines for the treatment of pleural empyema (10). As in our guidelines, given the decrease in the resistance of *S. pneumoniae* to amoxicillin after the implementation of PCV13, the use of 3GC in first-line treatment is also no more warranted, except in case of allergy. Nevertheless, they prefer a monotherapy with amoxicillin-clavulanate, when our guidelines propose amoxicillin in the absence of signs of severity or suspected *S. aureus* infection. Our choice was based on the fact that the use of amoxicillin-clavulanate also participates to the carriage of ESBL- producing gram-negative bacilli. While GAS and

S. pneumoniae account for more than half of the bacterial causes, and remain susceptible to amoxicillin in the current epidemiological situation. Nevertheless, we recommend a treatment with amoxicillin-clavulanate if there are arguments for *S. aureus* infection (i.e abscess …) or the presence of signs of severity. This question of the choice between amoxicillin or amoxicillin-clavulanate is well illustrated by the recent study of Leoni *et al* (21). They assessed, with the DELPHI method, practices of experts concerning the management of PE in France in 2018. They showed that the prescription of an intravenous monotherapy was consensual, however there was no consensus reached on the antibiotic to be used, amoxicillin or amoxicillin-clavulanate. Of note, in our study, the empiric treatment failures described in period 2 were not related with a *S. aureus* treated with amoxicillin, and also occurred with amoxicillin-clavulanate as first-line treatment. Thus, amoxicillin indications seemed well identified, and it allowed to avoid the prescription of amoxicillin-clavulanate for one third of patients. In presence of signs of severity, the GPIP always takes into account MRSA with a tritherapy composed by amoxicillin-clavulanate, clindamycin and vancomycin. Whereas in our guidelines we propose a tritherapy with amoxicillin-clavulanate, clindamycin and clarithromycin, which covers *M. pneumoniae.* Linezolid is only prescribed in case of suspected MRSA. That choice of empirical antibiotic should be guided by local epidemiology and local resistance data. In this study, there was only one MRSA in period 2 (which corresponds to one of the empiric treatment failures), without *Mycoplasma pneumoniae.* In the French study of Madhi *et al,* MRSA strains account for 17.6% of the causes of *S. aureus* infections, also without *M. pneumoniae* documentation (6). In addition, in a recent German study, MRSA and *M. pneumoniae* were documented in 10/488 and 2/488 children respectively (12). In a Norway study conducted after the implementation of PCV13, *M. pneumoniae* was the most frequently found bacteria (4/15 cases), although only in one case of complicated effusion, the others being associated with uncomplicated effusions (22). According to those data, this raises the question about the relevance of a macrolide, rather than vancomycin or linezolid, in presence of signs of severity,

even if MRSA is fairly rare in our area. Of note, in this study we observed that for patients with unfavourable evolution under amoxicillin-clavulanate, the antibiotic was modified for linezolid, in order to cover the SARM.

There was no significant difference in the mean antibiotic duration between the two periods (about 4 weeks). However, we found a significant decrease in the duration of intravenous antibiotics in period 2. We hypothesize that this could be explained in part by the decrease in the prescription of inflammatory blood tests after the implementation of the guidelines, the decision to switch to oral therapy being more based on clinical improvement, than on biological markers. No data are available to clearly recommend treatment duration, thus the GPIP recommends replacement with oral treatment and total duration depending on clinical progression, at 2–6 weeks (10).

Our work has several limitations. First, this was a retrospective study, resulting in missing data. Secondly, this study was a monocentric, with a small number of children in period 2. This was related to the limited inclusion period after the implementation of the guidelines. It was probably also related to the decrease in the incidence of PPE/PE, thanks to the generalization of the PCV13 in 2010 (5). Moreover, our results showed that children received significantly less NSAIDs in period 2 than in period 1. This could have an impact on our incidence: Le Bourgeois *et al* reported and increase risk of empyema for children with acute viral infections exposed to NSAIDs (23). Despite all, our population is similar to those of others studies of children hospitalized for community-acquired PPE/PE. Our median age is similar to those of the French study of Madhi *et al* (6) and the Canadian study of Haji *et al* (13), conducted in the same periods. In our study, the coverage with PCV13 was 84.6% among children in period 2, slightly less than the percentage of 92.2% reported by the national public health institute Santé Publique France among infants aged 24 months in 2017 (24). The proportion of children with previous medical history increased in period 2, because of more asthma. Similar finding has

been observed in a U.S study with children hospitalized for PE (7).

A pleural puncture was performed at diagnosis for slightly less than half of the children hospitalized. This rate is close to that observed in two other French studies, with a percentage between 30% and 51.7% depending on the year studied (6, 25). The overall detection rate of bacteria in blood and/or pleural fluid was 42.8 %. It is also comparable with the rates of 39.3% and 42% reported in the studies of Madhi *et al* (6) and Erlichman *et al* (19). This low rate can be explained in part by the initiation of antibiotic therapy in more than half of cases before the diagnosis of PPE/PE, a proportion also found in a French study (1). Thus, our results are concordant with literature, which supports the representativeness of our population.

As previously shown, the implementation of clinical practice guidelines is a powerful tool to modify and improve practices (26, 27). The implementation of these guidelines is a local collaborative work, which may explain this level of success. A large team of NUH medical staff (i.e pediatric pneumologists, pediatric infectious disease specialists, emergency physicians) were involved in generating recommendations and their diffusion. In the current context, such interventions that lowering the proportion of broad-spectrum antibiotic prescriptions need to be mainstreamed to preserve antimicrobials for future use (28).

In conclusion, the implementation in 2015 of the guidelines for the management of community-acquired PPE/PE at the NUH was associated with a significant decrease in the prescription of 3GC, without discernible increase in the morbidity. The relative increase in *S. aureus* and GAS infections required to consider these species when choosing empiric antibiotic therapy, especially in presence of toxin-related features. In this study the empiric prescription of amoxicillin in the absence of signs of severity or suspected *S. aureus* infection did not result in therapeutic failures. The question of covering the MRSA or *M. pneumoniae* in severe cases is still relevant, and requires multicentre and longer-term follow-up studies to respond.

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ANNEXES

Table 1 supp – Patients' characteristics according to the empiric antibiotic treatment, univariate analysis

Variables	3rd G Cephalosporin (N=118) n/N	Other antibiotic (N=27) n/N	*P*-Value
Age, months, median (IQR)	45.5 (26.3-78)	42 (24.5-89)	0.75
Gender, male, n (%)	66/118 (55.9)	13/27 (48.1)	0.46
Weight, kg, median (IQR)	16 (12 -21.4)	16.5 (11.5-25.3)	0.88
Previous medical history, n (%)	29/118 (24.6)	11/27 (40.7)	0.09
Underlying lung disease, n (%)	19/118 (16.5)	5/27 (18.5)	0.78
Preterm birth, n (%)	2/118 (1.7)	1/27 (3.7)	0.46
History of severe pulmonary infection, n (%)	0/118	1/27 (3.7)	0.19
Regular medical treatment, n (%)	16/118 (13.6)	8/27 (29.6)	0.08
Up-to-date vaccination, n (%)	37/58 (63.8)	8/15 (53.3)	0.46
Fully vaccinated with a PCV, n (%)	23/67 (34.3)	11/17 (64.7)	**0.023**
Drug allergy, n (%)	2/118 (1.7)	1/27 (3.7)	0.46
Previous treatment by NSAID, n (%)	49/118 (41.5)	1/27 (3.7)	**<0.001**
Previous treatment by corticosteroid, n (%)	9/118 (7.6)	2/27 (7.4)	1
Oxygen saturation at diagnosis, median (IQR)	96 (93-97)	95 (92-98)	0.62
Oxygen saturation < 92%, n (%)	16/105 (15.2)	5/24 (20.8)	0.54
O2 max at diagnosis, L/min, median (IQR)	1 (0.5-2)	1 (0.5-2)	0.84
FiO2 max, %, median (IQR)	47.5 (31.5-100)	40 (32.8-90)	1
Hypercapnia, n (%)	6/111 (5.4)	0/23	0.59
Hemodynamic failure, n (%)	9/118 (7.6)	1/27 (3.7)	0.69
Toxin-related signs, n (%)	6/118 (5.1)	4/27 (14.8)	0.091
Hemoptysis, n (%)	1/118 (0.8)	1/27 (3.7)	0.34
Hospital at diagnosis, NUH, n (%)	87/118 (73.7)	21/27 (77.8)	0.66
Initial Prescriber			
Pediatrician, n (%)	101/118 (85.6)	21/27 (77.8)	0.38
Pediatric critical care specialist, n (%)	12/118 (10.2)	5/27 (18.5)	0.32
Surgeon, n (%)	5/118 (4.2)	0/27	0.58
Initial prescription unit			
Emergency department, n (%)	61/118 (51.7)	15/27 (55.6)	0.72
Pediatric ward, n (%)	36/118 (30.5)	6/27 (22.2)	0.39
Resuscitation unit, n (%)	15/118 (12.7)	5/27 (18.5)	0.53
ICU, n (%)	0/118	1/27 (3.7)	0.19
Surgery department, n (%)	6/118 (5.1)	0/27	0.59

IQR, interquartile range; PCV, pneumococcal conjugate vaccine; O2, oxygen therapy; FiO2, fraction of inspired oxygen; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; NUH, Nantes University Hosptal; ICU, intensive care unit

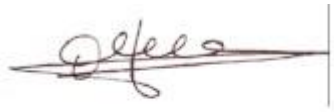
Table 2 supp - Description of patients with a change of empiric antibiotic treatment for treatment failure, period 2

Case	Age, months	Comorbidity	Fully vaccined	Empiric antibiotic treatment	Posology (mg/kg/j)	Mode	Duration before change (days)	Bacterial cause	Susceptibility	Cause of the antibiotic change	Secondarly prescribed antibiotic (duration after change, days)	Comment
1	2	No	yes	Amoxicillin-Clavulanate	150	IV	2	S. aureus (positive pleural culture)	Meticillin-resistant	Worsening of symptoms and abscess	Linezolid (21) + Cefotaxime (4)	Favourable evolution with linezolid
2	152	Asthma	no	Amoxicillin-Clavulanate	160	IV	14	S. pneumoniae (positive pleural Ag)	No data	Persistant fever at 14 days and increase in the volume of abscess	Linezolid (33)	Favourable evolution with linezolid
3	12	No	yes	Amoxicillin-Clavulanate + Clindamycin	150	IV	7 7	No identification		Persistant fever at 9 days	Macrolide (5) in adddition to Amox-Clav (35) + Clindamycin (7)	Apyrexia the day of macrolide addition
4	12	Epilepsia	no	Amoxicillin	250	oral	13	S. pneumoniae (positive blood culture)	Susceptible	Worsening of symptoms and increase in pleural effusion	Linezolid (10)	Favourable evolution with linezolid

Vu, le Président du Jury,

Professeur Elise LAUNAY

Vu, le Directeur de Thèse,



Docteur Myriam BENHAMIDA

Vu, le Doyen de la Faculté,

Professeur Pascale JOLLIET

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Titre de Thèse : IMPACT DE LA MISE EN PLACE EN 2015 DU PROTOCOLE SIMPLIFIE D'ANTIBIOTHERAPIE SUR LA PRESCRIPTION DE CEPHALOSPORINES DE 3ème GENERATION DANS LES PLEURO-PNEUMOPATHIES DE L'ENFANT AU CHU DE NANTES : ETUDE PLEURANTIB.

RESUME

Cette étude rétrospective et monocentrique évalue l'impact de la mise en place en 2015 du protocole simplifié d'antibiothérapie dans les pleuro-pneumopathies de l'enfant au CHU de Nantes. 129 enfants ont été inclus de 2003 à 2014 et 16 de 2016 à 2018. Le pourcentage de prescription de céphalosporines de 3ème génération (C3G) a significativement diminué (89,9% vs 12,5%, $p < 0,001$), tandis que ceux de l'amoxicilline et de l'amoxicilline-acide clavulanique ont augmenté de 7% à 31,2% ($p = 0,009$) et de 0,8% à 43,8% ($p < 0,001$) respectivement. Entre les deux périodes, il n'y avait pas de différence significative dans le pourcentage de changement d'antibiothérapie pour échec thérapeutique (18,6% vs 25%, p=0,51), ni dans la durée d'hospitalisation (13 jours vs 11,5 jours, p=0,21). Les pourcentages de *S. aureus* et *S. pyogenes* ont augmenté, respectivement de 5,7% à 33,3% (p=0,035) et de 9,4% à 33,3% (p=0,083). La mise en place du protocole simplifié d'antibiothérapie dans les pleuro-pneumopathies était associé à une diminution significative de la prescription de C3G, sans augmentation perceptible de la morbidité.

MOTS-CLES

Céphalosporines de 3ème génération, enfants, pleuro-pneumopathies, protocole, *S. pneumoniae*.