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UTILISATION DU LINEZOLIDE DANS LES PLEURO-PNEUMOPATHIES DE L'ENFANT : ETUDE RETROSPECTIVE ET MONOCENTRIQUE.

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SOMMAIRE

REMERCIEMENTS 2

TABLES DES ILLUSTRATIONS 4

INTRODUCTION 5

CONCLUSION 8

ARTICLE AU FORMAT PEDIATRIC PULMONOLOGY 11

ABSTRACT 12

ABBREVIATIONS 13

INTRODUCTION 14

MATERIALS AND METHODS 17

RESULTS 20

DISCUSSION 28

CONCLUSION 31

BIBLIOGRAPHIE 32

TABLES DES ILLUSTRATIONS

Table 1: Demographic, clinical, biological and bacteriological characteristics (1/2) 23

Table 1: Demographic, clinical, biological and bacteriological characteristics (2/2) 24

Table 2: Therapeutic characteristics 25

Table 3: Characteristics of treatment by linezolid 26

Table 4: Adverse events of linezolid 27

Supplemental table 1: Detailed comorbidities 35

INTRODUCTION

Le traitement des pleuro-pneumopathies sévères de l'enfant pose actuellement deux problématiques aux cliniciens : le choix d'une antibiothérapie probabiliste adaptée, mais aussi une modulation de la réponse inflammatoire afin d'en limiter les excès délétères. En effet, au cours de ces infections sévères, l'interaction entre la bactérie et le système immunitaire inné est modifiée, avec souvent au premier plan une réponse inflammatoire disproportionnée délétère (1). Sur le plan bactériologique, *Streptococcus pneumoniae*, *Streptococcus pyogenes* et *Staphylococcus aureus* sont les principaux agents responsables des pleuro-pneumopathies de l'enfant en France (2). Dans ce contexte, les dernières recommandations du Groupe de Pathologie Infectieuse Pédiatrique (GPIP) de juin 2016 préconisent en cas de pleuro-pneumopathie avec signes de gravité sans documentation, une triple antibiothérapie probabiliste à large spectre comportant de l'amoxicilline-acide clavulanique, de la vancomycine et de la clindamycine (3). En cas de pleuro-pneumopathie documentée à *Staphylococcus aureus* résistant à la méthicilline (SARM), l'antibiothérapie recommandée en première intention est la vancomycine associée à la clindamycine ou à la rifampicine (3).

L'amoxicilline-acide clavulanique appartient à la classe des béta-lactamines, la vancomycine à celle des glycopeptides. Ces deux classes d'antibiotiques agissent sur la paroi bactérienne, avec une bonne réponse bactériologique. Cependant la lyse bactérienne rapide qu'elles entrainent, participe à un relargage de nombreuses substances pro-inflammatoires (Pathogen Associated Molecular Patterns (PAMP)) (4). Par ailleurs la vancomycine ne s'administre que par voie intraveineuse, et du fait de sa fenêtre thérapeutique étroite, nécessite des dosages plasmatiques pour adapter sa posologie.

Le linézolide appartient à la classe des oxazolidinones et a été initialement développé comme alternative à la vancomycine dans les infections à *Staphylococcus aureus* résistant à la méticilline (SARM) (5). Son mode d'action particulier, comme inhibiteur de la synthèse protéique au niveau ribosomial, diminue le risque de résistance croisée avec les autres classes

d'antibiotiques. Il présente de plus une activité anti-toxinique, intéressante sur certaines souches de *Staphylocoque* ou de *Streptocoque A* (6). C'est un antibiotique temps dépendant, principalement bactériostatique, même s'il peut être bactéricide sur certaines souches de streptocoques, dont le pneumocoque (7). Sa biodisponibilité est équivalente entre la voie orale et intraveineuse, sa diffusion pulmonaire et pleurale est excellente. Pour le traitement des pleuro-pneumopathies, ses caractéristiques sont donc plus intéressantes que celles des bêta-lactamines.

Cependant, son profil de tolérance moins favorable que celui des bêta-lactamines et son activité sur des bactéries résistantes à la méticilline, en font une molécule réservée à des situations cliniques particulières, comme les infections cutanées à SARM (8). Il est aussi indiqué chez l'enfant, dans les infections à cocci gram positifs résistants, notamment dans les infections à entérocoque résistants à la vancomycine, et comme alternative à la vancomycine dans les pneumopathies à SARM, et pneumocoque multi-résistant (9–11).

Concernant la réponse inflammatoire, le linézolide réduit la sécrétion des facteurs de virulence dans des modèles de pneumopathies à SARM (12), du fait de son mode d'action sur la synthèse protéique. Il a aussi été montré que le linézolide a des propriétés immunomodulatrices *in vitro* avec une diminution en sa présence de la sécrétion d'IL-6, TNF-α et IL-1β par des monocytes stimulés par du lipopolysaccharide (LPS) (13).

Malgré ses atouts indéniables, le linézolide est peu prescrit dans les pleuro-pneumopathies de l'enfant, et il n'existe quasiment aucune donnée dans la littérature sur son utilisation dans cette indication. Seuls Kaplan et al. avaient 18 pleuro-pneumopathies traitées par linézolide, dont 9 drainées, dans leur série de 66 patients atteints de pneumopathie (14). Les pédiatres redoutent probablement ses effets secondaires à type de cytopénie et de neuropathie optique ou périphérique décrits lors d'une utilisation prolongée (15,16). Pourtant, plusieurs études ont montré que le linézolide n'entraînait pas plus d'effets secondaires que la vancomycine en population pédiatrique, pour une efficacité similaire (17,18).

Dans ce contexte, le linézolide est régulièrement utilisé au CHU de Nantes pour traiter des tableaux de pleuro-pneumopathies évoluant mal sous antibiothérapie de première intention. Mais il s'agit d'une indication hors AMM, et les dernières recommandations du Groupe de Pathologie Infectieuse Pédiatrique (GPIP) de juin 2016 n'évoquent l'usage du linézolide qu'en cas d'allergie à la vancomycine dans les pleuro-pneumopathies à SARM (3).

L'objectif principal de cette étude rétrospective était de déterminer la fréquence et l'indication de la prescription du linézolide dans le traitement de la pleuro-pneumopathie de l'enfant au CHU de Nantes entre décembre 2003 et novembre 2018.

Les objectifs secondaires étaient de déterminer le profil des patients traités par linézolide pour une pleuro-pneumopathie, de comparer leurs caractéristiques cliniques, biologiques et épidémiologiques à celles des patients traités par une autre antibiothérapie, et d'évaluer la tolérance clinico-biologique du linézolide dans cette indication.

CONCLUSION

Notre étude est la première à s'intéresser spécifiquement à l'utilisation du linézolide dans les pleuro-pneumopathies de l'enfant. Sur les 156 enfants hospitalisés au CHU de Nantes pour cette infection entre décembre 2003 et novembre 2018, 37 (23.7%) ont reçu du linézolide. La médiane d'âge des patients traités par linézolide était de 36 mois (interquartile range (IQR) : 12-125 mois), 57% étaient des garçons. La médiane d'âge des 66 enfants inclus par Kaplan et al. (14) dans l'étude sur les pneumopathies communautaires traitées par linézolide était similaire : 3 ans.

Pour 33 patients (89,2%) de notre étude, il s'agissait d'un traitement de seconde intention. Parmi eux, 18 enfants (55%) ont reçu du linézolide après l'échec du traitement initial, tandis que pour 10 autres patients (30%), il s'agissait d'un changement d'antibiothérapie sur avis d'experts. Seuls 4 patients (10,8%) ont reçu du linézolide en traitement de première ligne. Dans ce cas, il s'agissait de situations cliniques bien particulières : patients atteints de mucoviscidose, de leucémie aigue lymphoblastique ou de pleuro-pneumopathie avec abcès.

La prescription de linézolide était toujours réalisée par un pédiatre expert et majoritairement par un infectiologue (70.3%). Le traitement a été administré uniquement per os chez 15 enfants (40.5%), en intraveineux exclusif pour 7 patients (18.9%), et en intraveineux puis en per os chez les 15 autres patients (40.5%). Les médianes de posologie et de durée d'antibiothérapie par linézolide étaient respectivement de 30 mg/kg/jour (IQR 30-30) et de 16 jours (IQR 13-26). La posologie retrouvée dans notre étude est la même (30 mg/kg/jour) que celle utilisée par Kaplan et al. pour le traitement des infections à bactéries gram positives résistantes (19). Aucune donnée n'est disponible dans la littérature concernant la posologie recommandée du linézolide pour traiter une pleuro-pneumopathie chez l'enfant.

S'il n'y avait pas de différence significative sur le plan démographique et biologique entre les patients traités par linézolide et ceux traités par une autre antibiothérapie, ceux traités par linézolide présentaient globalement des tableaux plus sévères que les seconds, avec un taux

d’hospitalisation en soins intensifs/réanimation de 62.2% contre 43.7% (p=0.0496) et une hospitalisation plus longue : 16 (IQR 12-23) contre 12 jours (IQR 7-15 jours, p= 0.0005). Dans le groupe linézolide, les patients ont eu significativement plus de drainage pleural : 64.9% vs 44.5% (p=0.031), plus de drainage d’abcès pulmonaire : 13.5% vs 1.7% (p=0.009) et de vidéothoracoscopie : 21.6% vs 8.4% (p=0.039). Les patients traités par linézolide étaient significativement plus longtemps intubés: 29,5 jours (IQR 29,25-29,75) contre 6 jours (IQR 1-11,5), p=0,030. Ils nécessitaient significativement plus longtemps une nutrition parentérale : 10 jours (IQR 8-20) vs 8 jours (IQR 6-11.5), p=0.045.

La documentation bactériologique a été significativement plus obtenue dans le groupe linézolide (62,2%) que dans l'autre groupe (39,5%) (p=0,015). *Staphylococcus aureus* a été significativement plus documenté dans le groupe traité par linézolide (26,1 % vs 2,1 %, p=0,015), nous avons trouvé 3 SARM soit 13% des bactéries documentées dans ce groupe.

Des effets secondaires cliniques ont été retrouvés chez 8 patients (21.6%) traités par linézolide (tableau 4). Ce résultat est similaire à celui observé par Jantausch et al. (19.4%) (18). L'effet indésirable clinique le plus fréquent constaté dans notre étude était la diarrhée (10,8%), comme dans l'étude de Saiman et al. (10.8%) (17). Les autres effets secondaires cliniques retrouvés dans notre étude étaient des nausées (5.4%), des vomissements (2.7%) et une décoloration des dents (2.7%). 21,6% des patients présentaient un effet secondaire biologique du linézolide. Dans la majorité des cas, il s'agissait d'une anémie (18,9%), taux similaire à celui décrit dans l’étude de Jantausch et al. (18) : 23,5%. Aucun patient de notre étude n’a présenté de neutropénie contrairement à l’étude de Kaplan et al. (14), qui en retrouvait une chez 6.4% des patients. Le linézolide a été arrêté chez un enfant devant une anémie à 6,6 g/dl. Ce patient a reçu ce traitement par voie intraveineuse pendant 10 jours à une dose de 30 mg/kg/jour. Le linézolide avait été prescrit après l'échec de la première antibiothérapie. Cet enfant avait bénéficié de 2 drainages pleuraux en raison d'une mauvaise tolérance respiratoire. Au moment du diagnostic, l'hémoglobine était de 10,5 g/dl, 2 mois

après l'arrêt du linézolide, elle était remontée à 10,3 g/dl sans traitement médical ni transfusion.

Aucun patient n'a présenté d'effet indésirable irréversible tel qu'une neuropathie optique ou périphérique mais ces derniers sont décrits après 28 jours ou plus de linézolide dans la littérature (16) et la médiane de durée de traitement dans notre étude était de 16 jours (IQR 13-26).

La force de notre étude est d'être la première à décrire les caractéristiques démographiques, cliniques, biologiques, bactériologiques et thérapeutiques d'une population d'enfants hospitalisés et traités par linézolide pour une pleuro-pneumopathie. La première limite de notre travail est son caractère rétrospectif et monocentrique. La seconde concerne la population de l'étude via un probable biais de sélection. En effet, il est possible que nous ayons manqué certains patients du fait d'erreur de codage. La dernière limite est le faible effectif (37 patients traités par linézolide), il s'agit néanmoins de l'étude avec le plus grand nombre d'enfants traités par linézolide dans cette indication.

Au total, près d'un quart (23.7%) des enfants hospitalisés pour une pleuro-pneumopathie au CHU de Nantes entre 2003 et 2018 ont reçu du linézolide. Il s'agissait de patients avec comorbidités ou de tableau clinique sévère évoluant mal sous une première ligne d'antibiothérapie. Le profil de tolérance est similaire à celui décrit dans la littérature, nous n'avons pas observé d'effet secondaire grave irréversible. Cette étude montre que le linézolide pourrait être considéré comme une option thérapeutique de seconde ligne dans cette indication, en alternative à la vancomycine. Néanmoins sa prescription doit être réalisée sur avis de pédiatres experts, avec une vigilance quant à ses effets secondaires.

ARTICLE AU FORMAT PEDIATRIC PULMONOLOGY

TITLE PAGE

TITLE

Linezolid for the treatment of pleural empyema in hospitalized children.

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KEY WORDS

Pleural empyema, child, linezolid, antibiotherapy.

ABSTRACT

OBJECTIVES To determine the frequency and indication of linezolid in childhood pleural empyema at Nantes University Hospital.

To compare the clinical, biological and epidemiological characteristics of patients treated with linezolid with those of patients treated with other antibiotics, and to assess clinical and biological tolerance of linezolid in this indication.

STUDY POPULATION AND DESIGN All children hospitalized with a pleural empyema diagnosis in the Nantes University Hospital from December 2003 to November 2018 were included in this retrospective study.

RESULTS On 156 children hospitalized for pleural empyema, 37 (23.7%) received linezolid. For 33 patients (89.2%), it was a second-line treatment. 18 children (48.6%) received linezolid after failure of the initial therapy, for 10 other patients (27%) it was a change on the advice of experts.

Patients treated with linezolid were significantly more hospitalized in pediatric intensive care unit (PICU): 62.2% vs 43.7% (p = 0.0496) and their hospitalization was significantly longer: 16 (IQR 12-23) versus 12 days (IQR 7-15), p=0.0005.

In the linezolid group, patients had significantly more pleural drainage: 64.9% vs 44.5% (p=0.031), more pulmonary abscess drainage: 13.5% vs 1.7% (p=0.009) and more videothoracoscopy: 21.6% vs 8.4% (p=0.039).

8 patients (21.6%) presented clinical adverse events, 8 patients (21.6%) presented biological ones. Treatment was discontinued in one patient due to anemia that corrected without transfusion.

CONCLUSIONS Linezolid could be considered as a second-line treatment option in childhood pleural empyema, provided that it is prescribed on the advice of expert pediatricians in specific cases.

ABBREVIATIONS

ECMO	Extracorporeal Membrane Oxygenation
GPIP	Pediatric Infectious Pathology Group
IQR	Interquartile Range
IV	Intravenous
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NUH	Nantes University Hospital
PCV	Pneumococcal Conjugate Vaccine
PICU	Pediatric Intensive Care Unit
PMSI	Medical Program of Information System
MRSA	Methicillin-Resistant Staphylococcus Aureus

INTRODUCTION

The treatment of severe childhood pleural empyema currently poses two problems for clinicians: the choice of a suitable probabilistic antibiotic therapy, but also the modulation of the inflammatory response in order to limit harmful excesses. Indeed, in these severe infections, the interaction between the bacterium and the innate immune system is modified, often with a disproportionately harmful inflammatory response in the forefront (1). From a bacteriological point of view, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus* are the main agents responsible for childhood pleural empyema in France (2). In this context, the Pediatric Infectious Pathology Group (GPIP) recommended in June 2016, for the treatment of pleural empyema with signs of severity, a triple broad-spectrum probabilistic antibiotherapy including amoxicillin-clavulanic acid, vancomycin and clindamycin (3). In case of documented methicillin-resistant *Staphylococcus aureus* (MRSA) pleural empyema, the first-line antibiotic therapy recommended is vancomycin in combination with clindamycin or rifampicin (3).

Amoxicillin-clavulanic acid belongs to the beta-lactam class, vancomycin to the glycopeptide class. These two classes of antibiotics act on the bacterial wall, with a good bacteriological response. However, the rapid bacterial lysis that they cause, participates in the release of many pro-inflammatory substances (Pathogen Associated Molecular Patterns, (PAMP)) (4). Furthermore, vancomycin is only administered intravenously, and because of its narrow therapeutic window, its dosage requires to be adjusted with blood level.

Linezolid belongs to the oxazolidinone class and was originally developed as an alternative to vancomycin in MRSA infections (5). Its particular mode of action, as an inhibitor of protein synthesis at the ribosomal level, reduces the risk of cross-resistance with other classes of antibiotics. It also has an antitoxin activity, which is of interest on certain strains of *Staphylococcus* or *Streptococcus A* (6).

Linezolid is a time-dependent antibiotic, mainly bacteriostatic, even though it can be bactericidal on certain strains of streptococci, including the pneumococcus (7). Its bioavailability is equivalent between the oral and intravenous route and its pulmonary and pleural diffusion is excellent. For the treatment of pleural empyema, its characteristics are therefore more interesting than those of beta-lactams.

However, linezolid's less favorable tolerance profile, compared to beta-lactams', and its activity on methicillin-resistant bacteria, restrict it to specific clinical situations, such as MRSA skin infections (8). Linezolid is also indicated for resistant gram-positive cocci infections in children, particularly in vancomycin-resistant enterococcal infections, and as an alternative to vancomycin in MRSA pneumonia and multi-resistant pneumococcus (9-11).

In terms of inflammatory response, due to its mode of action on protein synthesis, linezolid reduces the secretion of virulence factors in certain models of MRSA pneumonitis (12). It has also been shown to have immunomodulatory properties in vitro, with a decrease of IL-6, TNF-α and IL-1β secretions in its presence, due to monocytes stimulated by lipopolysaccharide (LPS) (13).

Despite its undeniable advantages, linezolid is rarely prescribed in childhood pleural empyema, and there is very little data on its use in this indication in the literature. Kaplan et al. had 18 patients with pleural effusion, 9 of whom were drained, in their series of 66 pneumopathy patients treated with linezolid published in 2001 (14). Pediatricians probably fear its side effects such as a cytopenia and an optic or peripheral neuropathy described during prolonged treatment (15,16). However, several studies have shown that linezolid had no more side effects than vancomycin in the pediatric population, for similar efficiency (17,18).

In this context, linezolid is regularly used at Nantes University Hospital (NUH) on the advice of pediatric infectious diseases experts, to treat pleural empyema when it develops badly under first-line antibiotic therapy. However, this is an off-label use, and the latest recommendations of the Pediatric Infectious Pathology Group (GPIP) of June 2016 only mention the prescription of linezolid in cases of allergy to vancomycin in MRSA pleural empyema (3).

The main objective of this study was to determine the frequency and indication of linezolid prescription in the treatment of childhood pleural empyema at Nantes University Hospital between December 2003 and November 2018.

The secondary objectives were to determine the profile of patients treated with linezolid for pleural empyema, compare the clinical, biological and epidemiological characteristics of patients treated with linezolid to those of patients treated with other antibiotics, and assess clinical and biological tolerance of linezolid in this indication.

MATERIALS AND METHODS

STUDY POPULATION AND DESIGN

This was a monocentric and retrospective study. We included all children hospitalized in the NUH from December 2003 to November 2018 with a pleural empyema diagnosis defined by the following codes of the Medical Program of Information System (PMSI): J85, J85.1, J85.2, J86.0, J86.9. Codes J85, J85.1, J85.2 correspond to a lung abscess, J86.0 and J86.9 to a pyothorax. We excluded non-infectious pleural effusion and coding errors.

Data were tabulated using Excel (Microsoft, Inc, Redmond, USA). For our study, we followed the SQUIRE guidelines.

The project has been approved by the ethics in health committee of Nantes on the 3rd of April, 2019.

DEMOGRAPHIC, CLINICAL, BIOLOGICAL AND BACTERIOLOGICAL CHARACTERISTICS

The following demographic characteristics were collected in the medical records: age, gender, weight, medical history, administration of non-steroidal anti-inflammatory drugs or corticoids in the days before pleural empyema. Clinical and biological characteristics were sought at the diagnosis of pleural empyema or at admission to the NUH in case of transfer from another hospital. Clinical characteristics recorded were hypercapnia, hemodynamic instability, toxic symptoms, hemoptysis, and oxygen saturation. Hypercapnia was defined by a venous $PCO2 \geq 6.7$ kPa (standards of the hospital). Hemodynamic instability was defined by vascular filling or using amines. Toxic symptoms were defined by diarrhea and/or cutaneous rash. Biological characteristics collected were white blood cells, neutrophils, CRP and PCT. The methods to obtain bacteriological documentation and the characteristics of bacteria isolates were recorded.

THERAPEUTIC CHARACTERISTICS

Length of hospital stay, hospitalization on Pediatric Intensive Care Unit (PICU), use and length of antibiotherapy, oxygen therapy, non-invasive ventilation, intubation, pleural drainage, extracorporeal membrane oxygenation (ECMO), central venous route, enteral and parenteral nutrition as well as pleural puncture, bronchoscopy, videothoracoscopy, thoracotomy, intrapleural injection of urokinase and death were collected. Each length was expressed in days.

LINEZOLID

Patients were classified in the "linezolid" group if they had received this antibiotic for at least 48 hours. For patients treated by linezolid, were collected: indication, initial prescriber, initial prescribing service, routes of administration, dosage and length.

ADVERSE EVENTS OF LINEZOLID

We searched for all linezolid adverse events previously described in pediatric studies (9,10,15-18): diarrhea, nausea, vomiting, headache, optic or peripheral neuropathy, serotonin syndrome, oral candidiasis, rash, discolouration of the teeth, anemia, leucopenia, neutropenia, thrombocytopenia, eosinophilia, lactic acidosis. Anemia, leucopenia and thrombocytopenia were defined as <75% of the lower limit of the normal range (LLN) while neutropenia was defined as <50% of LLN for absolute neutrophil counts. These definitions were used in other pediatric studies on linezolid (17,19). Lactic acidosis was defined by a venous pH $\leq$ 7.35 and a hyperlactatemia > 2.4 mmol/L (standards at NUH).

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. All statistical tests were two-sided, with P values of ≤ 0.05 considered statistically significant. Statistical analyses were performed using R version 3.6.1.

RESULTS

PATIENTS CHARACTERISTICS

Between December 2003 and November 2018, 171 patients had a code consistent with pleural empyema. 15 coding errors occurred. Hence, our study included 156 children hospitalized at NUH for a pleural empyema. Of the 156 patients, 37 children (23.7%) received linezolid.

The median age of these children was 36 months (IQR 12-125), 56.7% were male, 32.4% had comorbidity. The underlying diseases of the patients included are precisely described in the supplemental table 1.

COMPARISON OF THE 2 GROUPS

There was no significant difference between patients treated with linezolid and those treated with other antibiotics about age, gender, presence of comorbidity or clinical and biological characteristics at diagnosis (table 1). 2 patients (5.4%) in the linezolid group had hemoptysis, none in the other group. NSAIDs use was significantly less frequent in the linezolid group (16.2%) than in the other group (37.8%), p=0.014.

Bacteriological documentation was significantly more obtained in the linezolid group (62.2%) than in the other group (39.5%), p=0.015. *Streptococcus pneumoniae* and *Streptococcus pyogenes* were significantly less common in the linezolid group than in the other antibiotics group, respectively: 56.5% vs 74.5%, p=0.015; 4.4% vs 14.9%, p=0.015. *Staphylococcus aureus* was significantly more observed in the linezolid group (26.1% vs 2.1%, p=0.015). 3 MRSA were isolated in the linezolid group and none in the other group. The three "other" bacteria isolated were *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Streptococcus intermedius*. In the linezolid group, bacteria were mostly found in pleural fluid (60.9%), by culture (58.8%).

We observed that 62.2% of the linezolid group were hospitalized in PICU, compared to 43.7% for the other antibiotics group, p = 0.0496 (table 2). Patients treated with linezolid stayed significantly longer in hospital: 16 days (IQR 12-23) vs 12 days (IQR 7-15), p=0.0005, and in PICU: 8 days (IQR 5-11) vs 4 days (IQR 2-8), p=0.003. In the linezolid group, patients had significantly more pleural drainage: 64.9% vs 44.5% (p=0.031), more pulmonary abscess drainage: 13.5% vs 1.7% (p=0.009) and more videothoracoscopy: 21.6% vs 8.4% (p=0.039). They also tended to benefit more from bronchoscopy: 8.1% vs 1.7% (p=0.087) and thoracotomy: 5.4% vs 0.8% (p=0.140). Enteral nutrition was significantly more often prescribed in the linezolid group: 32.4% versus 10.1% (p=0.001). There was no significant difference in the rate of parenteral nutrition between the two groups. Nevertheless, the length of parenteral nutrition was significantly longer for patients treated with linezolid: 10 days (IQR 8-20) vs 8 days (IQR 6-11.5), p=0.045. Patients treated with linezolid were intubated significantly longer: 29.5 days (IQR 29.25-29.75) vs 6 days (IQR 1-11.5), p=0.030. They also tended to receive non-invasive ventilation longer: 10 days (IQR 8-12) vs 2 days (IQR 1.75-2.75), p=0.060.

No patient had received an intrapleural injection of urokinase. In the linezolid group, one patient had received ECMO (2.7%), another patient died (2.7%).

LINEZOLID

For 33 patients (89.2%), linezolid was a second-line treatment (table 3). 18 children (48.6%) received linezolid after failure of the initial therapy, while for 10 other patients (27%) it was a change on the advice of experts.

Only 4 patients (10.8%) had received Linezolid as first-line therapy. This occurred in very specific situations: 2 patients had underlying condition (cystic fibrosis, acute lymphoblastic leukemia), and the 2 others had pleural empyema with abscess.

Linezolid had always been prescribed by an expert pediatrician, and mostly by an infectious disease specialist (70.3%). This antibiotic was started in PICU only for 32.4% of the patients.

It was an oral administration for 15 patients (40.5%). Continuous intravenous therapy was administered in 13 patients (35.1%) and discontinuous in 9 patients (24.3%). Dosage and length medians of linezolid were respectively 30 mg/kg/day (IQR 30-30) and 16 days (IQR 13-26).

Between the periods 2004-2009 and 2012-2018, a significant upward trend in the prescription of linezolid/pleural empyema was observed (p=0.022). Meanwhile the prescription of vancomycin/pleural empyema tended to decrease significantly (p=0.027). We also observed a significant trend of increasing numbers of *Staphylococcus aureus*/pleural empyema (p=0.014).

Among the 23 patients treated with linezolid with a bacterial documentation, *Streptococcus pneumoniae* was found in 13 children (56.5%). Of these 13 patients, 7 had a stop of the linezolid and switch for another antibiotherapy during the hospitalization, the other 6 received linezolid as exit therapy. Among the 6 patients discharged on linezolid, we noted 2 abscesses, 2 intermediate sensitivities to amoxicillin, 1 pleural empyema (with bacteremia) worsening on amoxicillin (250 mg/kg/day), 1 patient with documentation by soluble antigen and therefore without antibiogram.

Clinical adverse events were found in 8 patients (21.6%). 4 had diarrhea (10.8%), 2 had nausea (5.4%), 1 had vomiting (2.7%), and 1 had tooth discoloration (2.7%) (table 4). Biological side effects were found in 8 children (21.6%): 7 of them had anemia (18.9%) and one had lactic acidosis (2.7%). We noted one discontinuation of linezolid (2.7%) due to anemia (6.6 g/dl). This patient received linezolid intravenously for 10 days at a dose of 30 mg/kg/day. It was prescribed after the first treatment failed. This child had benefited from 2 pleural drainages due to poor respiratory tolerance. At diagnosis, hemoglobin was 10.5 g/dl, 2 months after stopping linezolid it was 10.3 g/dl.

Table 1: Demographic, clinical, biological and bacteriological characteristics (1/2)

Variable n (%), median [IQR] (/n=number of available answers if different of N =)	**Total** N=156	**Linezolid** N=37	**Other antibiotics** N=119	**p**
Demographic characteristics				
Age (months)	45.50 [25.75-85.25]	36 [12-125]	48 [30-82]	0.224
Male	85 (54.5)	21 (56.7)	64 (53.7)	0.751
Comorbidity ≥ 1	49 (31.4)	12 (32.4)	37 (31.1)	0.878
NSAIDs	51 (32.7)	6 (16.2)	45 (37.8)	0.014
Corticoids	11 (7.1)	2 (5.4)	9 (7.6)	1
Clinical presentation				
Hypercapnia	9 (6.3)	3 (8.8)	6 (5.5)	0.441
Hemodynamic instability	12 (7.7)	2 (5.4)	10 (8.4)	0.733
Hemoptysis	2 (1.3)	2 (5.4)	0	0.055
Toxic symptoms	10 (6.4)	1 (2.7)	9 (7.6)	0.454
Oxygen saturation	96 [93-98]	96 [94-98]	96 [92-97]	0.646
Biological characteristics at diagnosis				
WBC (cells/mm3)	18 500 [12 000-26 000]	18 250 [12 250-27 500]	18 500 [12 000-24 500]	0.529
Neutrophils (cells/mm3)	13 000 [8 000-20 000]	12 100 [7 925-17 775]	14 500 [8 000-20 600]	0.262
CRP (mg/L)	237.3 [121-322]	236 [97.5-320]	243 [137.5-324.8]	0.611
PCT (µg/L)	6.03 [0.79-14.28]	6.05 [0.83-14.7]	6 [0.77-13]	0.614
Bacteriological documentation	70 (44.9)	23 (62.2)	47 (39.5)	0.015
Streptococcus pneumoniae	48 (68.6)	13 (56.5)	35 (74.5)	0.015
Streptococcus pyogenes	8 (11.4)	1 (4.4)	7 (14.9)	
Staphylococcus aureus	7 (10)	6 (26.1)	1 (2.1)	
Others	7 (10)	3 (13)	4 (8.5)	

Table 1: Demographic, clinical, biological and bacteriological characteristics (2/2)

Variable n (%), median [IQR] (/n=number of available answers if different of N =)	**Total** N=156	**Linezolid** N=37	**Other antibiotics** N=119	**p**
Bacteria detected in				
Blood culture	8/70 (11.4)	4/23 (17.4)	4/47 (8.5)	0.637
Pleural fluid	45/70 (64.3)	14/23 (60.9)	31/47 (66)	
Blood culture and pleural fluid	8/70 (11.4)	3/23 (13)	5/47 (10.6)	
Others	9/70 (12.9)	2/23 (8.7)	7/47 (14.9)	
Means of documentation in pleural fluid				
Culture	25/53 (47.2)	10/17 (58.8)	15/36 (41.7)	0.082
Soluble antigen	14/53 (26.4)	3/17 (17.6)	11/36 (30.6)	
PCR	6/53 (11.3)	4/17 (23.5)	2/36 (5.6)	
Several bacterial tests	6/53 (11.3)	0	6/36 (16.7)	
Evocative direct examination	2/53 (3.8)	0	2/36 (5.6)	

Abbreviations: IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; WBC, white blood cells

Table 2: Therapeutic characteristics

Variable n (%), median [IQR]	Total N=156	Linezolid N=37	Other antibiotics N=119	p
Length of hospital stay (days)	12.5 [9-17]	16 [12-23]	12 [7-15]	0.0005
Hospitalization on PICU	75 (48.1)	23 (62.2)	52 (43.7)	0.0496
Length (days)	5 [2-10]	8 [5-11]	4 [2-8]	0.003
Oxygen therapy	117 (75)	27 (73)	90 (75.6)	0.744
02 (L/min)	1 [1-2]	1 [1-2]	1 [1-1.875]	0.182
Length (days)	7 [4-11]	9 [5-14.5]	7 [4-10]	0.084
Non-invasive ventilation	6 (3.9)	2 (5.4)	4 (3.4)	0.628
Length (days)	3.5 [2-5.75]	10 [8-12]	2 [1.75-2.75]	0.060
Intubation	11 (7.1)	2 (5.4)	9 (7.6)	1
Length (days)	8.5 [1-12.75]	29.5 [29.25-29.75]	6 [1-11.5]	0.030
Pleural puncture	71 (45.5)	17 (46)	54 (45.4)	0.952
Pleural drainage	77 (49.4)	24 (64.9)	53 (44.5)	0.031
Abscess	7 (4.5)	5 (13.5)	2 (1.7)	0.009
Bronchoscopy	5 (3.2)	3 (8.1)	2 (1.7)	0.087
Videothoracoscopy	18 (11.5)	8 (21.6)	10 (8.4)	0.039
Thoracotomy	3 (1.9)	2 (5.4)	1 (0.8)	0.140
Central venous route	74 (47.4)	22 (59.5)	52 (43.7)	0.094
Nutrition				
Enteral	24 (15.4)	12 (32.4)	12 (10.1)	0.001
Length (days)	12.5 [7-18]	12.5 [9.25-16.5]	12 [7-21]	0.772
Parenteral	52 (33.3)	13 (35.1)	39 (32.8)	0.790
Length (days)	9 [7-13.25]	10 [8-20]	8 [6-11.5]	0.045
Length of antibiotherapy (days)	33 [24.5-42]	31 [22-39]	34 [26.25-42]	0.337

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit

Table 3: Characteristics of treatment by linezolid

Variable n (%), median [IQR]	
Prescription of linezolid	37
Indication	
First-line	
Empiric therapy	4 (10.8)
Second-line	
Failure of initial therapy	18 (48.6)
Change on the advice of experts	10 (27)
Resistant bacteria on the antibiogram	4 (10.8)
Unknown	1 (2.7)
Prescriber	
Pediatric infectious diseases specialist	26 (70.3)
Pediatric pulmonologist	7 (18.9)
Intensive care pediatrician	4 (10.8)
Initial prescribing unit	
General pediatric unit	13 (35.1)
Intensive care unit	12 (32.4)
Surgery pediatric unit	7 (18.9)
Pediatric emergency department	4 (10.8)
Pediatric oncology unit	1 (2.7)
Routes of administration	
Oral	15 (40.5)
Intravenous	7 (18.9)
Intravenous, then oral	15 (40.5)
Dosage (mg/kg/day)	30 [30-30]
Maximum dosage (mg/kg/day)	40
Number of administrations (/day)	3 [2-3]
Total length of treatment (days)	16 [13-26]
Oral (days)	13 [4-18]
Intravenous (days)	5 [0-10]

Table 4: Adverse events of linezolid

Variable n (%)	N=37
Adverse events	
Clinical	8 (21.6)
Diarrhea	4 (10.8)
Nausea	2 (5.4)
Vomiting	1 (2.7)
Reversible tooth discoloration	1 (2.7)
Biological	8 (21.6)
Anemia	7 (18.9)
Lactic acidosis	1 (2.7)
Discontinuation of linezolid due to drug-related adverse events	1 (2.7)

DISCUSSION

This is the first study focused on the use of linezolid in childhood pleural empyema. We observed that linezolid was prescribed in almost a quarter of cases of childhood pleural empyema hospitalized in NUH between November 2003 and December 2018. This antibiotic had always been prescribed by an expert pediatrician and mostly by an infectious disease specialist (70.3%). In our study, linezolid was most commonly administered 3 times daily at 30 mg/kg/day as in study of Kaplan et al. (19). No data are available in the literature regarding the recommended dosage of linezolid for the treatment of childhood pleural empyema. The median age of our patients was similar to that of the children included by Kaplan et al. (14): 36 months and 3 years, respectively.

In our study, there were no significant differences between the two groups in terms of demographic and biological characteristics at diagnosis. However, patients treated with linezolid were more severe than those treated with other antibiotics: they were significantly longer hospitalized, intubated, and fed parenterally than patients in the other group. In addition, they had benefited significantly more frequently from pleural drainage, pulmonary abscess drainage, videothoracoscopy, enteral nutrition and were significantly more often hospitalized in PICU. The study of Le bourgeois et al. (20) showed that NSAIDs use during acute viral infection was associated with an increased risk of empyema in children. However, the severity of the patients treated by linezolid was not associated to NSAIDs use. Indeed, they had received NSAIDs significantly less frequently.

We know that the incidence and the bacterial ecology of childhood pleural empyema has completely changed in France since vaccination with pneumococcal conjugate vaccine (PCV) 13 as in the study of Ouldali et al. (21). *Staphylococcus aureus* was isolated from 6 patients (26%) treated with linezolid in our study, including 3 MRSA. However, the most frequently found bacterium was *Streptococcus pneumoniae* (56.5%). Linezolid was most often stopped when this bacterium was identified. This antibiotic was continued in case of pneumococcus

with decreased sensitivity to amoxicillin or in case of severe disease with failure of first-line treatment. In our study, since vaccination with PCV13, the proportion of *Staphylococcus aureus* pleural empyema and the prescription of linezolid increased. Linezolid seems to replace vancomycin in this indication at NUH. Indeed, while the prescription of linezolid increased, that of vancomycin decreased in our study. At NUH, we follow the GPIP recommendations for first-line treatment of the childhood pleural empyema. However, we frequently prescribe linezolid as a second-line treatment and not only in case of MRSA. This choice of antibiotherapy is probably made under the assumption of a benefit from the anti-inflammatory effects of linezolid. A multicentric study is needed to confirm the results observed in our hospital.

Regarding the safety of linezolid, we found 21.6% of clinical adverse events. This result is similar to that observed by Jantausch et al. (19.4%) (18). The most common clinical side effect found in our study was diarrhea (10.8%) as in the study of Saiman et al. (10.8%) (17). 21.6% of patients had a biological side effect of linezolid but in the majority of cases it was an anemia. We found 18.9% anemia, Jantausch et al. (18) had 23.5% in their study. We noted one discontinuation of linezolid (2.7%) due to anemia (6.6 g/dl), a serious but reversible adverse event. Our study didn’t show any patient with neutropenia, unlike the study by Kaplan et al. (14), which showed neutropenia in 6.4% of patients. No neuropathy, serotonin syndrome or other serious irreversible adverse events have occurred. These results can be explained by a low number of patients. No neuropathy was observed, but the median duration of linezolid was 16 days (IQR 13-26) while neuropathies are described after 28 days of treatment (16).

The strength of our study is to be the first to describe the demographic, clinical, biological, bacteriological and therapeutic characteristics of a population of children treated with linezolid specifically for a pleural empyema. Kaplan et al. included 18 infectious pleural effusion among the 66 patients in their study (14). One study reported 2 cases of severe childhood pleural empyema that were cured by linezolid (22). The first limit of our work is the small number of patients (37 patients treated with linezolid). However, this is the study with the largest number of children treated with this antibiotic for a pleural empyema and our patients were in the same ages as those in higher-powered studies of linezolid in other indications (9). The second limit is a retrospective, monocentric design. Some data were inaccurate in patient records, others were missing. The last concerns the study population via a probable selection bias. Indeed, coding errors are frequent, so we may have missed some inclusions.

CONCLUSION

Our study is the first to focus on the use of linezolid in childhood pleural empyema. Almost a quarter (23.7%) of children hospitalized for a pleural empyema at NUH between 2003 and 2018 received linezolid. It was a second-line treatment in the vast majority of cases (89.2%). The 2 most frequent indications were “failure of initial therapy” (48.6%) and “change on the advice of experts” (27%). Patients treated with linezolid were more severe than children treated with other antibiotics. In our study, we found the common and known clinical and biological side effects of linezolid such as diarrhea, nausea and anemia. However, no serious and irreversible adverse events had occurred.

Linezolid could be a second-line treatment option in childhood pleural empyema, provided that it is prescribed on the advice of expert pediatricians in very specific cases and that you are aware of the possible occurrence of side effects.

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Supplemental table 1: Detailed comorbidities

Variable n (%)	Total N=156	Linezolid N=37	Other antibiotics N=119
Comorbidity ≥ 1	49 (31)	12 (32)	37 (31)
History of severe respiratory infection	4	1	3
Asthma	23	3	20
Cystic fibrosis	1	1	0
Tuberculosis	1	0	1
Prematurity < 37 SA	5	2	3
Chronic neurological disease	6	2	4
Chronic nephrological disease	4	1	3
Congenital heart disease	2	1	1
Hirschsprung disease	1	0	1
Sickle cell anemia	1	0	1
Leukemia	1	1	0

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RESUME

Objectifs : Déterminer la fréquence et l'indication de la prescription du linézolide dans le traitement des enfants hospitalisés pour une pleuro-pneumopathie au CHU de Nantes entre décembre 2003 et novembre 2018. Les objectifs secondaires étaient de comparer les caractéristiques cliniques, biologiques et épidémiologiques des patients traités par linézolide à celles des patients traités par une autre antibiothérapie, et d'évaluer la tolérance clinique et biologique du linézolide dans cette indication.

Matériel et méthodes : Tous les enfants hospitalisés pour une pleuro-pneumopathie au CHU de Nantes de décembre 2003 à novembre 2018 ont été inclus dans cette étude rétrospective.

Résultats : Notre étude a porté sur 156 enfants, 37 (23,7 %) avaient reçu du linézolide. Pour 33 patients (89,2 %), il s'agissait d'un traitement de deuxième intention. 18 enfants (48,6 %) ont reçu du linézolide après l'échec du traitement initial, pour 10 autres patients (27 %), il s'agissait d'un changement d'antibiothérapie sur avis d'experts.
Les enfants traités par linézolide ont été significativement plus hospitalisés en soins intensifs/réanimation: 62,2 % vs 43,7 % (p = 0,0496) et leur hospitalisation était significativement plus longue : 16 jours (IQR 12-23) vs 12 jours (IQR 7-15), p=0,0005.
Dans le groupe linézolide, les patients ont eu significativement plus de drainage pleural : 64,9% vs 44,5% (p=0,031), plus de drainage d'abcès pulmonaires : 13,5% vs 1,7% (p=0,009) et de vidéothoracoscopie : 21,6% vs 8,4% (p=0,039). 8 patients (21,6 %) ont présenté des effets secondaires cliniques, 8 autres (21,6 %) des effets secondaires biologiques. Le linézolide a été arrêté chez un patient pour une anémie à 6.6 g/dl qui s'est spontanément corrigée. Aucun effet secondaire grave irréversible n'a été retrouvé.

Conclusion : Le linézolide pourrait être considéré comme un traitement de deuxième ligne de la pleuro-pneumopathie de l'enfant, à condition qu'il soit prescrit sur avis de pédiatres experts, dans des cas très spécifiques.

MOTS-CLES

PLEURO-PNEUMOPATHIES, ENFANTS, LINEZOLIDE, ANTIBIOTHERAPIE.