Année 2020/2021 N°

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

Par

Maya SROUR

Née le 07/02/1990 à Toulouse (31)

Efficacité et sécurité de la poursuite ou non du salbutamol inhalé après introduction du salbutamol intraveineux dans la prise en charge de seconde ligne de l'asthme aigu grave de l'enfant : une étude rétrospective bicentrique

---

Présentée et soutenue publiquement le **04 octobre 2021** devant un jury composé de :

Président du Jury : Professeur François LABARTHE, Pédiatrie, Faculté de Médecine -Tours

Membres du Jury :

Professeur Stéphane DAUGER, Réanimation pédiatrique, Faculté de Médecine – Paris VII

Professeur Antoine GUILLON, Médecine intensive - Réanimation, Faculté de Médecine - Tours

Docteur Annie-Laure SUC, Neuropédiatrie et handicaps, PH, CHU - Tours

Docteur Julie CHANTREUIL, Réanimation pédiatrique, PH, CHU - Tours

Docteur Isabelle GIBERTINI, Pédiatrie, PH, CHU - Tours

Directeur de thèse : Docteur Charlotte IDIER, Réanimation pédiatrique, PH, CHU – Tours

UNIVERSITE DE TOURS
FACULTE DE MEDECINE DE TOURS

DOYEN
Pr Patrice DIOT

VICE-DOYEN
Pr Henri MARRET

ASSESSEURS
Pr Denis ANGOULVANT, *Pédagogie*
Pr Mathias BUCHLER, *Relations internationales*
Pr Theodora BEJAN-ANGOULVANT, *Moyens – relations avec l'Université*
Pr Clarisse DIBAO-DINA, *Médecine générale*
Pr François MAILLOT, *Formation Médicale Continue*
Pr Patrick VOURC'H, *Recherche*

RESPONSABLE ADMINISTRATIVE
Mme Fanny BOBLETER

****

DOYENS HONORAIRES
Pr Emile ARON (†) – *1962-1966*
Directeur de l'Ecole de Médecine - 1947-1962
Pr Georges DESBUQUOIS (†) - *1966-1972*
Pr André GOUAZE (†) - *1972-1994*
Pr Jean-Claude ROLLAND – *1994-2004*
Pr Dominique PERROTIN – *2004-2014*

PROFESSEURS EMERITES
Pr Daniel ALISON
Pr Gilles BODY
Pr Jacques CHANDENIER
Pr Philippe COLOMBAT
Pr Etienne DANQUECHIN-DORVAL
Pr Pascal DUMONT
Pr Dominique GOGA
Pr Gérard LORETTE
Pr Dominique PERROTIN
Pr Roland QUENTIN

PROFESSEURS HONORAIRES
P. ANTHONIOZ – P. ARBEILLE – A. AUDURIER – A. AUTRET – P. BAGROS – P.BARDOS – C. BARTHELEMY – J.L. BAULIEU – C. BERGER – JC. BESNARD – P. BEUTTER – C. BONNARD – P. BONNET – P. BOUGNOUX – P. BURDIN – L. CASTELLANI – A. CHANTEPIE – B. CHARBONNIER – P. CHOUTET – T. CONSTANS – P. COSNAY – C. COUET – L. DE LA LANDE DE CALAN – J.P. FAUCHIER – F. FETISSOF – J. FUSCIARDI – P. GAILLARD – G. GINIES – A. GOUDEAU – J.L. GUILMOT – O. HAILLOT – N. HUTEN – M. JAN – J.P. LAMAGNERE – F. LAMISSE – Y. LANSON – O. LE FLOCH – Y. LEBRANCHU – E. LECA – P. LECOMTE – AM. LEHR-DRYLEWICZ – E. LEMARIE – G. LEROY – M. MARCHAND – C. MAURAGE – C. MERCIER – J. MOLINE – C. MORAINE – J.P. MUH – J. MURAT – H. NIVET – L. POURCELOT – P. RAYNAUD – D. RICHARD-LENOBLE – A. ROBIER – J.C. ROLLAND – D. ROYERE - A. SAINDELLE – E. SALIBA – J.J. SANTINI – D. SAUVAGE – D. SIRINELLI – J. WEILL

PROFESSEURS DES UNIVERSITES - PRATICIENS HOSPITALIERS

ANDRES Christian...Biochimie et biologie moléculaire
ANGOULVANT Denis...Cardiologie
APETOH Lionel...Immunologie
AUPART Michel..Chirurgie thoracique et cardiovasculaire
BABUTY Dominique..Cardiologie
BAKHOS David...Oto-rhino-laryngologie
BALLON Nicolas...Psychiatrie ; addictologie
BARILLOT Isabelle..Cancérologie ; radiothérapie
BARON Christophe...Immunologie
BEJAN-ANGOULVANT Théodora.........................Pharmacologie clinique
BERHOUET Julien..Chirurgie orthopédique et traumatologique
BERNARD Anne..Cardiologie
BERNARD Louis..Maladies infectieuses et maladies tropicales
BLANCHARD-LAUMONNIER Emmanuelle.......Biologie cellulaire
BLASCO Hélène..Biochimie et biologie moléculaire
BONNET-BRILHAULT Frédérique.....................Physiologie
BOURGUIGNON Thierry.......................................Chirurgie thoracique et cardiovasculaire
BRILHAULT Jean..Chirurgie orthopédique et traumatologique
BRUNEREAU Laurent...Radiologie et imagerie médicale
BRUYERE Franck..Urologie
BUCHLER Matthias..Néphrologie
CALAIS Gilles...Cancérologie, radiothérapie
CAMUS Vincent..Psychiatrie d'adultes
CORCIA Philippe..Neurologie
COTTIER Jean-Philippe..Radiologie et imagerie médicale
DEQUIN Pierre-François.....................................Thérapeutique
DESOUBEAUX Guillaume.....................................Parasitologie et mycologie
DESTRIEUX Christophe..Anatomie
DIOT Patrice...Pneumologie
DU BOUEXIC de PINIEUX Gonzague...............Anatomie & cytologie pathologiques
DUCLUZEAU Pierre-Henri....................................Endocrinologie, diabétologie, et nutrition
EL HAGE Wissam...Psychiatrie adultes
EHRMANN Stephan..Médecine intensive – réanimation
FAUCHIER Laurent...Cardiologie
FAVARD Luc..Chirurgie orthopédique et traumatologique
FOUGERE Bertrand..Gériatrie
FOUQUET Bernard...Médecine physique et de réadaptation
FRANCOIS Patrick..Neurochirurgie
FROMONT-HANKARD Gaëlle...............................Anatomie & cytologie pathologiques
GATAULT Philippe...Néphrologie
GAUDY-GRAFFIN Catherine.................................Bactériologie-virologie, hygiène hospitalière
GOUPILLE Philippe..Rhumatologie
GRUEL Yves..Hématologie, transfusion
GUERIF Fabrice..Biologie et médecine du développement et de la reproduction
GUILLON Antoine...Médecine intensive – réanimation
GUYETANT Serge...Anatomie et cytologie pathologiques
GYAN Emmanuel..Hématologie, transfusion
HALIMI Jean-Michel..Thérapeutique
HANKARD Régis...Pédiatrie
HERAULT Olivier..Hématologie, transfusion
HERBRETEAU Denis...Radiologie et imagerie médicale
HOURIOUX Christophe..Biologie cellulaire
IVANES Fabrice..Physiologie
LABARTHE François..Pédiatrie
LAFFON Marc...Anesthésiologie et réanimation chirurgicale, médecine d'urgence
LARDY Hubert..Chirurgie infantile
LARIBI Saïd..Médecine d'urgence
LARTIGUE Marie-Frédérique............................Bactériologie-virologie
LAURE Boris...Chirurgie maxillo-faciale et stomatologie
LECOMTE Thierry...Gastroentérologie, hépatologie
LESCANNE Emmanuel...Oto-rhino-laryngologie
LINASSIER Claude...Cancérologie, radiothérapie
MACHET Laurent...Dermato-vénéréologie
MAILLOT François...Médecine interne
MARCHAND-ADAM Sylvain..............................Pneumologie

MARRET Henri ....Gynécologie-obstétrique
MARUANI Annabel ....Dermatologie-vénéréologie
MEREGHETTI Laurent ....Bactériologie-virologie ; hygiène hospitalière
MITANCHEZ Delphine...Pédiatrie
MORINIERE Sylvain ....Oto-rhino-laryngologie
MOUSSATA Driffa...Gastro-entérologie
MULLEMAN Denis...Rhumatologie
ODENT Thierry..Chirurgie infantile
OUAISSI Mehdi ....Chirurgie digestive
OULDAMER Lobna...Gynécologie-obstétrique
PAINTAUD Gilles ....Pharmacologie fondamentale, pharmacologie clinique
PATAT Frédéric ....Biophysique et médecine nucléaire
PERROTIN Franck ....Gynécologie-obstétrique
PISELLA Pierre-Jean ....Ophtalmologie
PLANTIER Laurent ....Physiologie
REMERAND Francis..Anesthésiologie et réanimation, médecine d'urgence
ROINGEARD Philippe ....Biologie cellulaire
ROSSET Philippe ....Chirurgie orthopédique et traumatologique
RUSCH Emmanuel...Epidémiologie, économie de la santé et prévention
SAINT-MARTIN Pauline ....Médecine légale et droit de la santé
SALAME Ephrem...Chirurgie digestive
SAMIMI Mahtab..Dermatologie-vénéréologie
SANTIAGO-RIBEIRO Maria ....Biophysique et médecine nucléaire
THOMAS-CASTELNAU Pierre ....Pédiatrie
TOUTAIN Annick...Génétique
VAILLANT Loïc ....Dermato-vénéréologie
VELUT Stéphane ....Anatomie
VOURC'H Patrick...Biochimie et biologie moléculaire
WATIER Hervé ....Immunologie
ZEMMOURA Ilyess ....Neurochirurgie

PROFESSEUR DES UNIVERSITES DE MEDECINE GENERALE

DIBAO-DINA Clarisse
LEBEAU Jean-Pierre

PROFESSEURS ASSOCIES

MALLET Donatien ....Soins palliatifs
POTIER Alain...Médecine Générale
ROBERT Jean ....Médecine Générale

PROFESSEUR CERTIFIE DU 2ND DEGRE

MC CARTHY Catherine.......................................Anglais

MAITRES DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS

AUDEMARD-VERGER Alexandra ....Médecine interne
BARBIER Louise ....Chirurgie digestive
BINET Aurélien...Chirurgie infantile
BISSON Arnaud ....Cardiologie (CHRO)
BRUNAULT Paul ....Psychiatrie d'adultes, addictologie
CAILLE Agnès ....Biostat., informatique médical et technologies de communication
CARVAJAL-ALLEGRIA Guillermo ....Rhumatologie (au 01/10/2021)
CLEMENTY Nicolas..Cardiologie
DENIS Frédéric ....Odontologie
DOMELIER Anne-Sophie ....Bactériologie-virologie, hygiène hospitalière
DUFOUR Diane..Biophysique et médecine nucléaire
ELKRIEF Laure..Hépatologie – gastroentérologie
FAVRAIS Géraldine ....Pédiatrie
FOUQUET-BERGEMER Anne-Marie..................Anatomie et cytologie pathologiques
GOUILLEUX Valérie ....Immunologie
GUILLON-GRAMMATICO Leslie ....Epidémiologie, économie de la santé et prévention

HOARAU Cyrille ....Immunologie
LE GUELLEC Chantal ....Pharmacologie fondamentale, pharmacologie clinique
LEFORT Bruno ....Pédiatrie
LEGRAS Antoine ....Chirurgie thoracique
LEMAIGNEN Adrien ....Maladies infectieuses
MACHET Marie-Christine...................................Anatomie et cytologie pathologiques
MOREL Baptiste ....Radiologie pédiatrique
PARE Arnaud...Chirurgie maxillo-faciale et stomatologie
PIVER Éric ....Biochimie et biologie moléculaire
REROLLE Camille ....Médecine légale
ROUMY Jérôme ....Biophysique et médecine nucléaire
SAUTENET Bénédicte..Thérapeutique
STANDLEY-MIQUELESTORENA Elodie............Anatomie et cytologie pathologiques
STEFIC Karl ....Bactériologie
TERNANT David ....Pharmacologie fondamentale, pharmacologie clinique
VUILLAUME-WINTER Marie-Laure ....Génétique

MAITRES DE CONFERENCES DES UNIVERSITES

AGUILLON-HERNANDEZ Nadia ....Neurosciences
NICOGLOU Antonine ....Philosophie – histoire des sciences et des techniques
PATIENT Romuald..Biologie cellulaire
RENOUX-JACQUET Cécile ....Médecine Générale

MAITRES DE CONFERENCES ASSOCIES

BARBEAU Ludivine...Médecine Générale
ETTORI-AJASSE Isabelle...................................Médecine Générale
PAUTRAT Maxime ....Médecine Générale
RUIZ Christophe...Médecine Générale
SAMKO Boris ....Médecine Générale

CHERCHEURS INSERM - CNRS - INRAE

BECKER Jérôme ....Chargé de Recherche Inserm – UMR Inserm 1253
BOUAKAZ Ayache...Directeur de Recherche Inserm – UMR Inserm 1253
BRIARD Benoit ....Chargé de Recherche Inserm – UMR Inserm 1100
CHALON Sylvie ....Directeur de Recherche Inserm – UMR Inserm 1253
DE ROCQUIGNY Hugues....................................Chargé de Recherche Inserm – UMR Inserm 1259
ESCOFFRE Jean-Michel ....Chargé de Recherche Inserm – UMR Inserm 1253
GILOT Philippe ....Chargé de Recherche Inrae – UMR Inrae 1282
GOUILLEUX Fabrice ....Directeur de Recherche CNRS – EA 7501 - ERL CNRS 7001
GOMOT Marie..Chargée de Recherche Inserm – UMR Inserm 1253
HEUZE-VOURCH Nathalie ....Directrice de Recherche Inserm – UMR Inserm 1100
KORKMAZ Brice ....Chargé de Recherche Inserm – UMR Inserm 1100
LATINUS Marianne ....Chargée de Recherche Inserm – UMR Inserm 1253
LAUMONNIER Frédéric ....Chargé de Recherche Inserm - UMR Inserm 1253
LE MERREUR Julie ....Directrice de Recherche CNRS – UMR Inserm 1253
MAMMANO Fabrizio ....Directeur de Recherche Inserm – UMR Inserm 1259
MEUNIER Jean-Christophe ....Chargé de Recherche Inserm – UMR Inserm 1259
PAGET Christophe ....Chargé de Recherche Inserm – UMR Inserm 1100
RAOUL William ....Chargé de Recherche Inserm – UMR CNRS 1069
SI TAHAR Mustapha..Directeur de Recherche Inserm – UMR Inserm 1100
SUREAU Camille..Directrice de Recherche émérite CNRS – UMR Inserm 1259
WARDAK Claire...Chargée de Recherche Inserm – UMR Inserm 1253

CHARGES D'ENSEIGNEMENT

Pour l'Ecole d'Orthophonie
DELORE Claire ....Orthophoniste
GOUIN Jean-Marie..Praticien Hospitalier
Pour l'Ecole d'Orthoptie
BOULNOIS Sandrine ....Orthoptiste
SALAME Najwa ....Orthoptiste
Pour l'Ethique Médicale
BIRMELE Béatrice ....Praticien Hospitalier

« Choisissez un travail que vous aimez,
Et vous n’aurez pas à travailler un seul jour de votre vie. »

Confucius

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

REMERCIEMENTS

Aux membres du jury

A Monsieur le Professeur François LABARTHE
Je te remercie de me faire l'honneur d'être le président de ce jury de thèse, et de la simplicité et la gentillesse avec lesquelles tu m'as accueillie dans ton service alors que je n'étais qu'une jeune interne.

Au Docteur Charlotte IDIER
Un immense merci de la confiance que tu m'as accordée en me confiant ce travail, le premier que tu encadres et qui m'a passionnée; merci d'avoir été si patiente et indulgente, tu n'as pas eu l'élève la plus assidue ! Au plaisir de travailler de nouveau avec toi, et de retrouver très bientôt ta joie de vivre.

Au Docteur Annie-Laure SUC
Merci tout simplement d'être le médecin que tu es, la passion avec laquelle tu fais ce métier, tu es un véritable modèle pour nous tous. Je te souhaite maintenant de pouvoir te reposer tout autant que de profiter de tout ce dont tu as toujours rêvé, et que tu as mis de côté pour te consacrer pleinement à tes patients, petits et grands.

Au Docteur Julie CHANTREUIL
Merci pour tout ce que tu m'as transmis durant mon internat, ton exigence, ta confiance, et surtout ta grande bienveillance ; tu resteras certainement l'un des médecins qui m'auront le plus marquée et inspirée de toutes mes études. J'espère être à la hauteur de l'enseignement que tu m'as donné.

Au Docteur Isabelle GIBERTINI
Merci d'avoir accepté de faire partie de ce jury, et de la douceur avec laquelle tu m'as accueillie lorsque j'arrivais toute jeune interne au CHU.

A Monsieur le Professeur Stéphane DAUGER
Je vous remercie infiniment de me faire l'honneur de juger ce travail de thèse ; soyez assuré de toute ma gratitude et de mon profond respect.

A Monsieur le Professeur Antoine GUILLON
Je vous remercie infiniment d'avoir accepté de faire partie de ce jury de thèse, et de l'honneur que vous me faites de juger ce travail pédiatrique ; soyez assuré de tout mon respect.

Aux équipes médicales, merci pour l'enseignement que vous m'avez donné, votre douceur et votre bienveillance, j'espère être à la hauteur de tout ce que vous m'avez appris. Je ne vous oublierai pas.
A l'équipe de réanimation, Nicolas, Nadine, Claire et Léa, pour m'avoir si bien accueillie tant de fois auprès de vous, merci pour votre patience et votre bienveillance, et pour m'avoir donné le goût de la réanimation, je n'aurais pas pu rêver meilleure équipe pour finir cet internat.
A l'équipe de neuropédiatrie, Pr Castelnau, Maximilien, Marine, Elisabeth, Anne-Sophie (et bien sûr Emmanuelle et Marie-Anne), pour m'avoir transmis le goût de la neuropédiatrie et pour me faire l'honneur de m'accueillir dans votre équipe au mois de novembre, j'ai hâte de pouvoir encore apprendre à vos côtés.
A l'équipe des urgences, Yves, Annie, Nathalie, Sarah, Myriam, Laure, Marie, Laetitia, Karim, pour la bonne humeur avec laquelle vous m'avez accueillie durant trois mois, et pour être toujours à mon écoute.
A l'équipe de néphropédiatrie, Elodie, Violaine, Louis, pour votre gentillesse; et merci tout particulièrement à Sylvie pour ton aide précieuse dans la rédaction de mon mémoire.
A l'équipe de l'USP, Marine, Aurélie, Elisabeth, Laure, pour ce que vous m'avez appris ; merci tout particulièrement à Stéphanie, toi qui a su me faire aimer la gastropédiatrie alors que ça n'était pas gagné, merci pour ta bienveillance à mon égard et pour tout ce que tu m'as transmis.
A l'équipe de réanimation néonatale d'Orléans, Evelyne, Jean-Bosco, Nabil, Roselyne, Diana, Julie, Magalie, Marie, Chloé, Bérengère, pour être une si belle équipe.
Aux équipes de pédiatrie de Dreux et Orléans, merci de m'avoir soutenue durant mes premiers pas d'interne.

Aux équipes soignantes, que vous soyez infirmiers(ères), puéricultrices, aide-soignant(e)s, ASH et que j'ai eu la chance de croiser durant mon internat, vous avez tous et toutes contribué, chacun et chacune à votre manière, au médecin que je suis et que je serai demain.
A l'équipe de réanimation, l'une des plus merveilleuses que j'ai pu rencontrer, merci pour votre patience, votre soutien, et votre gentillesse ; merci pour vos sourires et votre joie de vivre, je suis heureuse de pouvoir continuer à travailler avec vous.
A l'équipe du SSR pour sa bonne humeur et son soutien sans faille (et pauses goûter, codes d'accès et bureau offerts lorsque j'errai dans les couloirs de Clocheville).
A l'équipe de neuropédiatrie pour son dévouement à toute épreuve et que je me fais une joie de retrouver bientôt.
Aux équipes des urgences pour leur gentillesse, et en particulier pour l'équipe de nuit et son soutien sans faille aux heures les plus sombres des gardes.
A l'équipe de néphropédiatrie pour sa douceur.
Merci aux autres, celles croisées ici et ailleurs, dont l'investissement et le désintéressement m'ont donné envie de travailler à l'hôpital.

Un merci tout particulier à Elisabeth, qui m'a donné envie de poursuivre dans cette voie à un moment où mes doutes prenaient le pas sur mes ambitions.

Table des matières

Liste des tableaux

Liste des figures

ARTICLE SCIENTIFIQUE

<u>Title</u>: Efficacy and safety of continuing or not continuing nebulized salbutamol after its intravenous introduction in the second-line management of pediatric acute severe asthma: a retrospective two-center study.

<u>Section</u>: Original article

Abstract word count: 383 words
60 references, 3704 words, 6 tables, 5 figures, 2 supplementary files

<u>Short title:</u> Second-line management of acute severe asthma in children

<u>Conflict of interest</u>: none

ABSTRACT

Background: While β2-mimetics are the cornerstone of treatment for severe acute asthma in children, the modalities of using IV salbutamol in second-line therapy remain under-investigated. The main objective was to compare the effectiveness of continuing or not continuing inhaled salbutamol after its IV introduction in the second-line treatment of pediatric acute severe asthma.

Methods: A retrospective French two-center study was conducted in children aged 28 days to 18 years with a diagnosis of severe acute asthma admitted between 2010 and 2021 to the Pediatric Intensive Care Units (PICUs) of Tours and Lille University Hospital. Demographic characteristics, asthma disease, and PICU stay data (e.g., ventilatory and hemodynamic support, lengths of stay, β2-mimetic-associated adverse events, follow-up after discharge) were collected from computerized patient records. The following endpoints were used to address the primary objective: hospitalization and PICU lengths of stay, characteristics of IV salbutamol use (duration and maximum dosage), duration of oxygen dependence and maximum partial pressure of CO2 (PCO2).

Results: A total of 95 patients were included in the group combining inhaled and IV salbutamol (IV/inhβ2+ - Tours University Hospital) and 114 patients in the group using IV salbutamol alone (IVβ2+ - Lille University Hospital) with a median age of 4 and 4.5 years, respectively. The two groups were broadly comparable in terms of demographic and clinical characteristics, reason for transfer to PICU, and severity on admission. The median PICU length of stay was 2.3 days in the IVβ2+ group versus 3 days in the IV/inhβ2+ group (p=0.003). Intravenous salbutamol treatment was used for a significantly shorter duration when used alone, with a median at 29.4 hours versus 47.4 hours in the IV/inhβ2+ group (p<0.001), and at a significantly lower maximum dosage: 1.1µg/kg/min versus 1.7µg/kg/min, respectively (p=0.001). The median duration of oxygen dependence was 26 hours in the IVβ2+ group versus 42.2 hours in the IV/inhβ2+ group (p=0.003). There was no significant difference between the two groups regarding total length of hospital stay and maximum PCO2.

Conclusion: This study provides a first estimate in favor of the lack of superior effectiveness of the continuation of nebulized salbutamol when it is initiated by IV route in the second-line treatment of children with acute severe asthma. Further prospective studies with larger sample sizes and standardized protocols are needed to determine the therapeutic value of this strategy.

Keywords: acute severe asthma, beta2-mimetics, salbutamol, nebulizations, intravenous, pediatric intensive care unit, ventilation, hemodynamic, safety

INTRODUCTION

Asthma is a major global health problem, affecting more than 300 million people worldwide. It is the most common chronic pediatric disease[1–3], ranking among the top 20 chronic conditions for disability-adjusted life years[4], with a mortality rate in children up to 0.7 per 100 000[5]. It is a complex and heterogeneous immune-mediated inflammatory process involving genetic predisposition, epigenetic changes and environmental triggers. Pathological consequences include airway reactivity, bronchospasm, mucosal swelling and mucus production, leading to airway resistance with reduced air flow[6,7]. Its evolution is characterized by exacerbations with non-specific symptoms, representing one of the main reasons for emergency room visits (up to 20% in autumn or winter), the leading cause of school absenteeism and the leading cause of hospitalization[8]. Secondary to a severe bronchial obstructive syndrome, status asthmaticus or severe asthma exacerbation, is defined by the *Société de Réanimation de Langue Française* (SRLF) as "an asthma exacerbation likely to be life-threatening and/or requiring urgent management"[9]. The pharmacodynamic properties of inhaled short-acting β2-agonists such as salbutamol[10] (short onset of action of few minutes with long duration of action ~4 – 6 hours) combined with their efficacy and safety profiles make them the cornerstone of treatment for acute exacerbations, intermittently or continuously, in combination with systemic steroids and anticholinergics, both in outpatient and inpatient settings[11–15].

To our knowledge, there is no clear recommendation on the use of adjunctive therapies in second-line management[16–20], such as intravenous (IV) β2-mimetics, leaving it to each Pediatric Intensive Care Unit (PICU) to determine the modalities for implementing therapeutic escalation[21,22]. Indeed, several French centers, such as ours in Tours, continue nebulizations after the introduction of IV salbutamol, while others such as Lille stop them. Although a synergistic or at least additional effect can be assumed when combining the two routes of administration, the usefulness of the inhaled route may nevertheless be questioned when major bronchospasm with bronchial obstruction could prevent the nebulized drug from reaching the airways. However, the few data available[23], especially in children[24–27], suffer from several limitations, such as small sample size[28–31], the absence of a comparator group[27,28], the use of surrogate endpoints[27,31,32], and the lack of safety data[30]. Finally, no study has compared the two approaches in a comprehensive manner, either in terms of hospitalization parameters, ventilator and/or hemodynamic support use.

Given the lack of clear guidance despite the high prevalence of status asthmaticus in children, its potential burden in terms of mortality and public health, and the common use of drugs with a narrow therapeutic index, an evaluation of this second-line management through the conduct of a French two-centre observational study seemed particularly relevant. The main objective was to compare the effectiveness of continuing (IV/inhβ2+ group) or not continuing (IVβ2+ group) inhaled salbutamol after its IV introduction in the second-line management of acute severe asthma in children. The secondary objectives were to describe the occurrence of complications and to assess the safety profile of each therapeutic strategy.

METHODS

Design and Settings

This observational and retrospective study was conducted in the two following French PICUs: Clocheville Hospital of Tours University Hospital and Jeanne de Flandre Hospital of Lille University Hospital.

Population

We collected data from all the children aged 28 days to 18 years with a diagnosis of status asthmaticus according to the SRLF criteria[9], admitted to a PICU at one of the participating centers, and requiring treatment with IV β2-mimetics. The doses used for IV salbutamol (continuous infusion) were the same in the two centers from 0.5 to 5µg/kg/min. In Tours University Hospital, the protocol for administration of nebulized salbutamol was 1.25mg to 5mg depending to age and/or weight.

As the expected number of patients was approximately 100 per group, patients were retrospectively included between January 01, 2010 (Tours) or January 01, 2012 (Lille) until January 01, 2021 (Tours and Lille).

If a child was eligible for the study for multiple stays, the first was included in the study. Children from Lille University Hospital who received both inhaled β2 and IV salbutamol were excluded as were those from Tours University Hospital who received IV salbutamol alone. Children whose families expressed their refusal, according to the procedure applicable at each center, were also excluded from the study.

Data source and collection

Data were collected by analyzing the history of computerized patient records.

The following data were extracted: demographic characteristics, familial and personal medical history especially for asthma (e.g., trigger(s), atopy), data of PICU stay (e.g., trigger, pre-hospital care, medical management, ventilation and hemodynamic supports), occurrence of β2-mimetics-associated adverse events, PICU and hospital lengths of stay and follow-up data such as recurrence after hospital discharge.

Objectives and Outcomes

The main objective was to compare the effectiveness of continuing (IV/inhβ2+ group) or not continuing (IVβ2+ group) inhaled salbutamol after the introduction of IV salbutamol in the second-line management of acute severe asthma in children in terms of duration of use and maximum dose of IV salbutamol, length of PICU stay, length of hospitalization, duration of oxygen dependence and maximum of partial pressure of CO_2 (PCO_2).

The secondary objectives were to describe the occurrence of complications, namely the use of third- and fourth- lines of treatment: ventilation support, hemodynamic support, hemofiltration, extracorporeal membrane oxygenation (ECMO) and to describe the occurrence of β2-mimetics-associated adverse events: tachycardia, hyperlactatemia (≥ 2 mmol/l), hypokaliemia (≤ 3.5 mmol/l), hyperglycemia (≥ 11 mmol/l) and tremors.

Our a priori hypothesis was that the combination of the two routes of administration would result in better efficacy but at the cost of a potentially less favorable safety profile.

Statistical analyses

Categorical variables are presented as absolute number (percentage). Continuous variables were described by the mean ± standard deviation (SD) in case of a normal distribution, or as median [interquartile range (IQR)] in the opposite case. The normality of the distributions was assessed graphically by histograms and Shapiro-Wilk test. Qualitative variables were compared by Chi-square or Fisher exact test as appropriate. The Mann-Whitney *U* test was used to compare continuous variables. Two-sided P values of less than 0.05 were considered to indicate statistical significance. SAS software (version 9.4) was used for the statistical analyses.

Ethical issues

The protocol was approved by the institutional review board of Tours University Hospital. The study was registered under number F20210813160008 in the data processing register and complies with the *Commission Nationale de l'Informatique et des Libertés (CNIL)*. Patients and their families were informed through posters available in the PICUs (**Supplementary Appendix 1**).

RESULTS

Demographic, familial and personal characteristics of the children

A total of 95 patients were included at Tours University Hospital (IV/inhβ2+ group) and 114 patients at Lille University Hospital (IVβ2+ group) (**Figure 1**).

Table 1 summarizes the characteristics of the children at inclusion. The male-to-female ratio was 1.21 in the IV/inhβ2+ group and 1.65 in the IVβ2+ group. No statistically significant difference was found between the two groups regarding familial and personal history of atopic disease. A total of 18% of children (17/94) in the IV/inhβ2+ group and 14% of those (16/114) in the IVβ2+ group were included for inaugural severe acute asthma (p=0.43).

Characteristics of the children at PICU admission

A trigger was found in 74% of cases (n=70) in the IV/inhβ2+ group versus 71% (n=81) in the IVβ2+ group (p=0.67), and was predominantly infectious in children at each center. The department of origin and reason(s) for transfer to PICU are shown in **Figures 2 and 3**.

Inhaled salbutamol was initiated by the family in 63% of children (58/92), including 36% (18/50) according to an available protocol in the IV/inhβ2+ group; and in 75% of children (83/111), including 46% (36/79) according to an available protocol in the IVβ2+ group (p=0.07 and p=0.28, respectively). There was no statistically significant difference in severity scores between the two groups. **Table 2** shows the main clinical and paraclinical characteristics of children at PICU admission.

Regarding medical care before PICU admission, nebulized β2-mimetics had already been initiated in 98% of cases (92/94) in the IV/inhβ2+ group and in 96% of cases (104/108) in the IVβ2+ group (p=0.69), mainly through a continuous delivery mode. Intravenous salbutamol had already been initiated for 47% (n=45) of children in the IV/inhβ2+ group versus 51% (n=58) in the IVβ2+ group (p=0.61). There was no statistically difference between the two groups with respect to respiratory, hemodynamic or anti-infectious supports.

One patient in the IVβ2+ group needed a cardiopulmonary resuscitation because of a cardiorespiratory arrest to management. **Table 3** displays characteristics of medical support at admission to PICU.

Primary objective

The median PICU length of stay was 2.3 days (IQR, 1.5-3.4) for the IVβ2+ group versus 3 days (IQR, 2-4.8) for the IV/inhβ2+ group (p=0.003). The median hospital length of stay was 6.6 days (IQR, 4.8-10.2) in the IVβ2+ group versus 6.2 days (IQR, 4.6-9) in the IV/inhβ2+ group (p=0.18). The duration of IV salbutamol use was significantly shorter when used alone with a median of 29.4 hours (IQR, 14.7-41.1) in the IVβ2+ group compared to 47.4 hours (IQR, 29-95) when nebulizations were continued (p<0.001). The maximum dosage was significantly lower (p=0.001) in the IVβ2+ group (1.1µg/kg/min; IQR, 0.7-2) than in the IV/inhβ2+ group (1.7µg/kg/min; IQR, 0.9-3). There was no significant difference in maximum PCO2 between the two groups. The median duration of oxygen dependence was significantly shorter (p=0.003) in the IVβ2+ group with a median of 26.0 hours (IQR, 11.9-

62.5) than in the IV/inhβ2+ group (median, 42.2 hours; IQR, 26-107.2). Primary outcomes are shown on **figures 4 and 5**.

Other features of second-line pharmacological support for children during their PICU stay are presented in **Table 4**.

Secondary objectives

Occurrence of complications

A total of 99% of children (n=94) in the IV/inhβ2+ group and 98% (n=112) in the IVβ2+ group required ventilatory support, mostly non invasive. Vascular filling was used in 33% of children (n=31) in the IV/inhβ2+ group versus 20% of those (n=23) in the IVβ2+ group (*p*=0.04). A total of 9% of children (n=9) in the IV/inhβ2+ group versus 6% of those (n=7) in the IVβ2+ group needed hemodynamic support by amines (*p*=0.37). ECMO was required in 1 and 2 patients from Tours and Lille centers, respectively. There was no statistically significant difference between the two groups concerning the occurrence of superinfection or secondary sepsis. Mortality rates were not statistically different (*p*=0.66) between the two groups: 3% (n=3) versus 2% (n=2) in IV/inhβ2+ group and IVβ2+ group, respectively. **Table 5** displays the occurrence of complications during the stay in PICU.

Safety profile of β2-mimetics

There was no significantly difference between the two groups in the occurrence of potentially β2-mimetics-related adverse events, with all children experiencing at least one (**Table 6**). The prevalence of tremor was not described because it was not reported in any patient in our cohort.

Follow-up of children after discharge from hospital

After discharge from the PICU, children were transferred to peripheral hospitals in 2% (2/92) of the IV/inhβ2+ group and 27% of the IVβ2+ group (30/112) (*p*<0.001). The episode leading to hospitalization motivated the initiation or modification of background therapy in 90% of patients (80/89) in the IV/inhβ2+ group and 86% of patients (77/90) in the IVβ2+ group (*p*=0.38).

A total of 91% of children (41/45) had a new exacerbation after discharge in the IV/inhβ2+ group and 93% (55/59) in the IVβ2+ group (*p*=0.69), requiring hospitalization in 50% (n=20/40) and 71% (36/51), respectively (*p*=0.05). For these patients, PICU admission was reported in 15% (n=6) of the IV/inhβ2+ group compared to 38% (n=20) of the IVβ2+ group (*p*=0.01).

DISCUSSION

In this real-life study comparing children who continued (n=95) or stopped (n=114) nebulized therapy after initiation of IV salbutamol in second-line treatment of severe acute asthma over a period of more than 10 years, discontinuation of nebulizations was associated with a significantly shorter PICU length of stay (p=0.03), duration of salbutamol IV use (p<0.001), lower maximum dose of IV salbutamol (p=0.001), and duration of oxygen dependence (p=0.003). Of note, the two groups were broadly comparable at inclusion, in terms of demographic characteristics, reason for transfer to PICU and clinical severity at admission (e.g., PIM3 and PELOD scores). Similarly, the variables relating to the characteristics of the asthmatic episode and/or the asthmatic disease were both balanced between the two groups and in agreement with the literature such as trigger which was mainly infectious, as already described for pediatric asthma exacerbations in general[33].

These results challenge the added value of combining the two routes of administration in severe exacerbations, as expressed in our hypothesis. This assumption was based on the substantial variability in the pharmacokinetics of nebulized salbutamol[34–36], especially since several bronchial obstruction makes drug deposition even unpredictable[28]. Other arguments for combining these two routes of administration were that nebulized salbutamol administration is safe, it is a well-approved route of administration in the literature[11,12,37], an additive effect is expected, and it is the route of administration clearly recommended by the SRLF[9]. In line with this hypothesis, several studies have found a gain in efficacy when the two routes are combined, as reported in a Cochrane review published in 2012[38]. Indeed, in a double-blind placebo-controlled randomized trial, Browne *et al.*, [24,25] showed that children receiving, in addition to nebulizations of salbutamol and corticosteroids, a single-dose IV salbutamol bolus within the first two hours of emergency department management of children with acute severe asthma (n=14), had a more rapid recovery time to discharge from the emergency department and the need for supplemental oxygen. Similarly, Bogie *et al.*,[26] found a trend toward improvement with the use of IV terbutaline in combination with continuous high-dose nebulized salbutamol, ipratropium, and systemic corticosteroids in a randomized double-blind trial in children aged 2 to 17 years. In addition, a study from 2006[31] showed that the response to IV terbutaline associated to continuous nebulized albuterol was significantly influenced by the use of a standardized protocol of administration, in terms of PICU length of stay and hospital costs.

In the light of our results, it nevertheless seems important to question the real interest of combining two routes of administration for the same drug. Indeed, it can be assumed that when administered IV at an effective dose, the reuptake of salbutamol by the lungs is sufficient to achieve a tissue concentration capable of inducing effective bronchodilation without the need for additional administration by nebulization, the limitations of which have been described above. Furthermore, the IV route appears as a safe route of administration when bronchospasm is major and the child's compliance not optimal, a frequent situation in cases of severe exacerbations, with sometimes very agitated children in whom "forced"

administration of aerosols may be difficult and have more risk than benefit (e.g., respiratory exhaustion, loss of vascular access). In addition, Cheong *et al.*[32] showed that nebulized salbutamol had significantly lower efficacy than a strategy with IV salbutamol after one nebulization of salbutamol in an add-on (nasal oxygen and hydrocortisone succinate) randomized double-blind trial in adults with severe acute asthma. The results of this study, as well as own, raise the question of a possible tachyphylaxis with compromised therapeutic effect as previously reported with the chronic administration of β2-agonists[39–41]. This hypothesis is supported by the fact that, in our study, the dosages of IV β2-mimetics were significantly lower when this route was used alone. In addition to its impact on the inter-individual phenotypic variability of asthma and especially on the response to IV β2-mimetics[42], the β2-adrenoreceptor polymorphisms (loci 16 and 27 gene)[43–46] have also been involved in this tachyphylaxis phenomenon[47,48]. Another hypothesis would be a loss of selectivity in case of high plasma concentration with a secondary activation of α1-adrenoreceptors of the smooth muscle of the airways, known to cause a bronchoconstriction[49] which could then reduce the effectiveness of the anti-asthmatic treatment.

On the other hand, while the average PICU length of stay was shorter in the center using only IV salbutamol (i.e., Lille), the overall length of stay was not significantly different between the two groups. Therefore, the children in Lille University Hospital were more likely to stay in a conventional ward, which can reduce in particular the risk of psychological impact inherent in a PICU stay on families. Nevertheless, this interpretation must be qualified, because we cannot exclude that the number of continuous monitoring beds available in conventional service was different between the two groups. Finally, the duration of oxygen dependence was significant shorter in the IVβ2+ group (26 hours, IQR 11.9-62.5) compared to the IV/inhβ2+ group (42.2 hours, IQR 26-107.2) (p=0.003), which may indirectly reflect earlier clinical respiratory improvement.

Regarding to our secondary objectives, there was no significant difference in the proportion of third- and fourth line treatments. Almost all the children received ventilatory support and whereas no statistical difference was found concerning non-invasive or invasive ventilation, patients, in the IVβ2+ group had significantly higher use of high-flow nasal cannula (HFNC) therapy compared with those in the IV/inhβ2+ group (71% versus 41% of cases, respectively; p<0.001), what can appear discordant with the idea that this way of ventilation facilitates the administration of aerosols; but during a shorter period and without any difference concerning maximal FiO2 (in our practice oxygen dependence is higher after nebulizations, although we found no data in the literature to support this finding). Several studies have highlighted the interest of the ventilatory support in severe acute asthma, decreasing signs of work of breathing such as respiratory rate, accessory muscle use, and dyspnoea with good safety and tolerability[50–55], but only one looked at its use with IV β2agonist[56], showing that early administration of continuous terbutaline could decrease the need for mechanical respiratory support. About hemodynamic support, in our study vascular filling was used more often in the IV/inhβ2+ group compared to the IVβ2+ group (p=0.041). Moreover, the recourse to ventilation and the type of hemodynamic support if needed also depend on practice patterns between centers and within centers between practitioners (e.g., systematic vascular filling at

admission like second line treatment or real necessity during the PICU stay because of a hemodynamic instability), so it is therefore difficult to draw a conclusion. There was no significant difference in the use of amines or ECMO. We did not found any statistically significant difference concerning mortality. However, it should be noted that our study was underpowered to compare these hard endpoints and the lack of literature on these parameters as evaluation criteria does not allow us to put them into perspective.
Concerning the safety profile, the combined use of both routes was associated with the higher prevalence of adverse events requiring specific treatment such as hypokalemia and hyperglycemia. Nevertheless, these results should be treated with caution. Indeed, biological adverse event duration (e.g., hyperlactatemia) was determined by the time between the date of the abnormal value and the date of the first normal value, thus depending of the frequency of biological monitoring. Hypokalemia was defined as potassium below 3.5mmol/l, but lead to specific management if below 3.5mmol/l in the IV/inhβ2+ group (consisting of IV refills of 1mEq/kg maximum 10mEq over 3 hours) and below 3mmol/l in the IVβ2+ group (consisting mainly of IV supplementation directly into the infusion, some cases of IV refills). Finally, data concerning the safety of β2-agonists in the literature are diverse and quite discordant[38,56,57].

Regarding to those considerations, however, it is clear that other factors must be taken into account when interpreting our results, such as the influence of the timing of care particularly IV salbutamol treatment, associated medical care or pre-hospital care. Firstly, in the studies that showed a benefit of IV salbutamol, it was introduced very early, sometimes as soon as the patient was admitted to the emergency department[24–26], which is very different from the practices studied in Tours and Lille; although we did not found any significantly difference between the two groups. Secondly, it seems that the time to medical referral was longer in Tours University Hospital, what means longer delay of medical management and therefore a higher risk of treatment failure; unless this is solely related to the smaller number of available peripheral hospitals. As an argument for an earlier management in Lille, 13% of patients (n=15) were transferred directly from home in the IVβ2+ group, compared to 2% (n=2) in the IV/inhβ2+ group (p<0.001). Concerning the medical management associated with IV salbutamol, it seems that during the pre-hospital management in Lille, other nebulizations (ipratropium) and administration of magnesium sulfate were more prevalent, which corresponds to a more optimal first-line management in accordance with the recommendations and could lead to an earlier improvement of the symptomatology. Finally, and although a reporting bias cannot be excluded, another important point concerned the existence of an available home exacerbation protocol, which was significantly higher in Lille than in Tours (63% versus 27% of patients, respectively). In addition, the existence of a background treatment was more frequently reported in Lille (68%) compared with Tours (51%). All these observations can be interpreted as if Lille patients were better supervised, which may have consequences on the speed of appropriate management in case of (severe) exacerbation.

The main limitations were our relative low sample size and biases linked to the retrospective nature of the study. It is also important to note that we collected data on non-standardized

management (e.g., biological monitoring) and that some variables of interest had missing data. For all these reasons, it is difficult to draw a definitive conclusion in terms of effectiveness even if this study provides a comprehensive picture that can support a prospective assessment of the comparative effectiveness of these two strategies. Further studies with larger samples sized evaluating strategies according to more standardized protocols for management (e.g., time to instauration, dosing) and assessment of the disease (e.g., Pediatric Respiratory Assessment Measure (PRAM)[58,59]; **Supplementary Appendix 2**) are needed to more reliably assess the superiority of one type of management in terms of effectiveness and safety.

CONCLUSION

This study, the first in the literature comparing the management of acute severe asthma between two French PICUs, provides a first estimate in favor of the lack of superior effectiveness of the continuation of nebulized salbutamol when it is initiated by IV route in the second-line treatment of children with acute severe asthma. Further prospective studies with standardized protocols are necessary to establish specific recommendations about the second-line treatment of acute severe asthma in children, whose impact in terms of morbidity, mortality and public care cost could be major.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2

2. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733-743. doi:10.1016/S0140-6736(06)69283-0

3. Xie M, Liu X, Cao X, Guo M, Li X. Trends in prevalence and incidence of chronic respiratory diseases from 1990 to 2017. *Respir Res*. 2020;21:49. doi:10.1186/s12931-020-1291-8

4. Serebrisky D, Wiznia A. Pediatric Asthma: A Global Epidemic. *Ann Glob Health*. 85(1):6. doi:10.5334/aogh.2416

5. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis*. 2014;18(11):1269-1278. doi:10.5588/ijtld.14.0170

6. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391(10122):783-800. doi:10.1016/S0140-6736(17)33311-1

7. Garden FL, Simpson JM, Mellis CM, Marks GB. Change in the manifestations of asthma and asthma-related traits in childhood: a latent transition analysis. *European Respiratory Journal*. 2016;47(2):499-509. doi:10.1183/13993003.00284-2015

8. Asthme. Accessed July 22, 2021. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/asthme

9. Le Conte P, Terzi N, Mortamet G, et al. Prise en charge de l'exacerbation sévère d'asthme. *Méd Intensive Réa*. 2020;29(2):43-64. doi:10.37051/mir-00011

10. Andrzejowski P, Carroll W. Salbutamol in paediatrics: pharmacology, prescribing and controversies. *Arch Dis Child Educ Pract Ed*. 2016;101(4):194-197. doi:10.1136/archdischild-2014-307285

11. WMS-French-Pocket-Guide-GINA-2016.pdf. Accessed July 22, 2021. https://ginasthma.org/wp-content/uploads/2016/09/WMS-French-Pocket-Guide-GINA-2016.pdf

12. Camargo CA, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev*. 2003;(4):CD001115. doi:10.1002/14651858.CD001115

13. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev*. 2013;(8):CD000060. doi:10.1002/14651858.CD000060.pub2

14. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2001;(1):CD000195. doi:10.1002/14651858.CD000195

15. Schuh S, Reisman J, Alshehri M, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med*. 2000;343(10):689-694. doi:10.1056/NEJM200009073431003

16. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2014;(5):CD010909. doi:10.1002/14651858.CD010909.pub2

17. Wong JJM, Lee JH, Turner DA, Rehder KJ. A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children. *Expert Rev Respir Med*. 2014;8(4):423-441. doi:10.1586/17476348.2014.915752

18. Rehder KJ. Adjunct Therapies for Refractory Status Asthmaticus in Children. *Respir Care*. 2017;62(6):849-865. doi:10.4187/respcare.05174

19. Carroll CL, Sala KA. Pediatric status asthmaticus. *Crit Care Clin*. 2013;29(2):153-166. doi:10.1016/j.ccc.2012.12.001

20. Nievas IFF, Anand KJS. Severe Acute Asthma Exacerbation in Children: A Stepwise Approach for Escalating Therapy in a Pediatric Intensive Care Unit. *J Pediatr Pharmacol Ther*. 2013;18(2):88-104. doi:10.5863/1551-6776-18.2.88

21. Boeschoten S, de Hoog M, Kneyber M, Merkus P, Boehmer A, Buysse C. Current practices in children with severe acute asthma across European PICUs: an ESPNIC survey. *Eur J Pediatr*. 2020;179(3):455-461. doi:10.1007/s00431-019-03502-9

22. Pardue Jones B, Fleming GM, Otillio JK, Asokan I, Arnold DH. Pediatric acute asthma exacerbations: Evaluation and management from emergency department to intensive care unit. *J Asthma*. 2016;53(6):607-617. doi:10.3109/02770903.2015.1067323

23. Starkey ES, Mulla H, Sammons HM, Pandya HC. Intravenous salbutamol for childhood asthma: evidence-based medicine? *Arch Dis Child*. 2014;99(9):873-877. doi:10.1136/archdischild-2013-304467

24. Browne GJ, Penna AS, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet*. 1997;349(9048):301-305. doi:10.1016/S0140-6736(96)06358-1

25. Browne GJ, Lam LT. Single-dose intravenous salbutamol bolus for managing children with acute severe asthma in the emergency department:Reanalysis of data. *Pediatr Crit Care Med*. 2002;3(2):117-123. doi:10.1097/00130478-200204000-00005

26. Bogie AL, Towne D, Luckett PM, Abramo TJ, Wiebe RA. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. *Pediatr Emerg Care*. 2007;23(6):355-361. doi:10.1097/01.pec.0000278397.63246.33

27. Stephanopoulos DE, Monge R, Schell KH, Wyckoff P, Peterson BM. Continuous intravenous terbutaline for pediatric status asthmaticus. *Crit Care Med*. 1998;26(10):1744-1748. doi:10.1097/00003246-199810000-00033

28. Williams S, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma? *Thorax*. 1977;32(5):555-558. doi:10.1136/thx.32.5.555

29. Williams SJ, Winner SJ, Clark TJ. Comparison of inhaled and intravenous terbutaline in acute severe asthma. *Thorax*. 1981;36(8):629-631. doi:10.1136/thx.36.8.629

30. Van Renterghem D, Lamont H, Elinck W, Pauwels R, Van der Straeten M. Intravenous versus nebulized terbutaline in patients with acute severe asthma; a double-blind randomized study. *Ann Allergy*. 1987;59(4):313-316.

31. Carroll CL, Schramm CM. Protocol-based titration of intravenous terbutaline decreases length of stay in pediatric status asthmaticus. *Pediatr Pulmonol*. 2006;41(4):350-356. doi:10.1002/ppul.20394

32. Cheong B, Reynolds SR, Rajan G, Ward MJ. Intravenous beta agonist in severe acute asthma. *BMJ*. 1988;297(6646):448-450. doi:10.1136/bmj.297.6646.448

33. Jartti T, Bønnelykke K, Elenius V, Feleszko W. Role of viruses in asthma. *Semin Immunopathol*. 2020;42(1):61-74. doi:10.1007/s00281-020-00781-5

34. Penna AC, Dawson KP. Nebulized salbutamol (albuterol): systemic absorption could be important in achieving bronchodilatation. *J Asthma*. 1993;30(2):105-107. doi:10.3109/02770909309054504

35. Penna AC, Dawson KP, Manglick P, Tam J. Systemic absorption of salbutamol following nebulizer delivery in acute asthma. *Acta Paediatr*. 1993;82(11):963-966. doi:10.1111/j.1651-2227.1993.tb12609.x

36. Janson C. Plasma levels and effects of salbutamol after inhaled or i.v. administration in stable asthma. *European Respiratory Journal*. 1991;4(5):544-550.

37. Salmeron S, Brochard L, Mal H, et al. Nebulized versus intravenous albuterol in hypercapnic acute asthma. A multicenter, double-blind, randomized study. *Am J Respir Crit Care Med*. 1994;149(6):1466-1470. doi:10.1164/ajrccm.149.6.8004299

39. Tellería JJ, Blanco-Quirós A, Muntión S, et al. Tachyphylaxis to beta2-agonists in Spanish asthmatic patients could be modulated by beta2-adrenoceptor gene polymorphisms. *Respir Med*. 2006;100(6):1072-1078. doi:10.1016/j.rmed.2005.09.028

40. Maconochie JG, Minton NA, Chilton JE, Keene ON. Does tachyphylaxis occur to the non-pulmonary effects of salmeterol? *Br J Clin Pharmacol*. 1994;37(2):199-204. doi:10.1111/j.1365-2125.1994.tb04261.x

41. Sears MR, Taylor DR. The beta 2-agonist controversy. Observations, explanations and relationship to asthma epidemiology. *Drug Saf*. 1994;11(4):259-283. doi:10.2165/00002018-199411040-00005

42. Carroll CL, Schramm CM, Zucker AR. Slow-responders to IV beta2-adrenergic agonist therapy: defining a novel phenotype in pediatric asthma. *Pediatr Pulmonol*. 2008;43(7):627-633. doi:10.1002/ppul.20846

43. Finkelstein Y, Bournissen FG, Hutson JR, Shannon M. Polymorphism of the ADRB2 gene and response to inhaled beta- agonists in children with asthma: a meta-analysis. *J Asthma*. 2009;46(9):900-905. doi:10.3109/02770900903199961

44. Liggett SB. Genetic variability of the β2 adrenergic receptor and asthma exacerbations. *Thorax*. 2006;61(11):925-927. doi:10.1136/thx.2006.064006

45. Carroll CL, Stoltz P, Schramm CM, Zucker AR. Beta2-adrenergic receptor polymorphisms affect response to treatment in children with severe asthma exacerbations. *Chest*. 2009;135(5):1186-1192. doi:10.1378/chest.08-2041

46. Carroll CL, Sala KA, Zucker AR, Schramm CM. Beta-adrenergic receptor polymorphisms associated with length of ICU stay in pediatric status asthmaticus. *Pediatr Pulmonol*. 2012;47(3):233-239. doi:10.1002/ppul.21544

47. Contopoulos-Ioannidis DG, Manoli EN, Ioannidis JPA. Meta-analysis of the association of β2-adrenergic receptor polymorphisms with asthma phenotypes. *Journal of Allergy and Clinical Immunology*. 2005;115(5):963-972. doi:10.1016/j.jaci.2004.12.1119

48. Larj MJ, Bleecker ER. Effects of beta2-agonists on airway tone and bronchial responsiveness. *J Allergy Clin Immunol*. 2002;110(6 Suppl):S304-312. doi:10.1067/mai.2002.130045

49. Reinhardt D. Adrenoceptors and the lung: their role in health and disease. *Eur J Pediatr*. 1989;148(4):286-293. doi:10.1007/BF00444116

50. Thill PJ, McGuire JK, Baden HP, Green TP, Checchia PA. Noninvasive positive-pressure ventilation in children with lower airway obstruction. *Pediatr Crit Care Med*. 2004;5(4):337-342. doi:10.1097/01.pcc.0000128670.36435.83

51. Mayordomo-Colunga J, Medina A, Rey C, et al. Non-invasive ventilation in pediatric status asthmaticus: a prospective observational study. *Pediatr Pulmonol*. 2011;46(10):949-955. doi:10.1002/ppul.21466

52. Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. *Ann Intensive Care*. 2017;7(1):55. doi:10.1186/s13613-017-0278-1

53. Pilar J, Modesto I Alapont V, Lopez-Fernandez YM, Lopez-Macias O, Garcia-Urabayen D, Amores-Hernandez I. High-flow nasal cannula therapy versus non-invasive ventilation in children with severe acute asthma exacerbation: An observational cohort study. *Med Intensiva*. 2017;41(7):418-424. doi:10.1016/j.medin.2017.01.001

54. Basnet S, Mander G, Andoh J, Klaska H, Verhulst S, Koirala J. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. *Pediatr Crit Care Med*. 2012;13(4):393-398. doi:10.1097/PCC.0b013e318238b07a

55. Carroll CL, Zucker AR. The increased cost of complications in children with status asthmaticus. *Pediatr Pulmonol*. 2007;42(10):914-919. doi:10.1002/ppul.20682

56. Doymaz S, Schneider J, Sagy M. Early administration of terbutaline in severe pediatric asthma may reduce incidence of acute respiratory failure. *Ann Allergy Asthma Immunol*. 2014;112(3):207-210. doi:10.1016/j.anai.2014.01.003

57. Abramson MJ, Walters J, Walters EH. Adverse effects of beta-agonists: are they clinically relevant? *Am J Respir Med*. 2003;2(4):287-297. doi:10.1007/BF03256657

58. Chiang VW, Burns JP, Rifai N, Lipshultz SE, Adams MJ, Weiner DL. Cardiac toxicity of intravenous terbutaline for the treatment of severe asthma in children: a prospective assessment. *J Pediatr*. 2000;137(1):73-77. doi:10.1067/mpd.2000.106567

59. Birken CS, Parkin PC, Macarthur C. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity, and responsiveness. *J Clin Epidemiol*. 2004;57(11):1177-1181. doi:10.1016/j.jclinepi.2004.02.016

60. Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr*. 2008;152(4):476-480, 480.e1. doi:10.1016/j.jpeds.2007.08.034

TABLES

Table 1 | Characteristics of children at inclusion	IV β2 + Inhaled β2 *(IV/inhβ2+)* n = 95	IV β2 *(IVβ2+)* n = 114	*p*-value
Demographical characteristics			
Sex, males, n (%)	52 (55)	71 (62)	0.27
Age, years, Median [IQR]	4.0 [1.4-8.2]	4.5 [1.9-10.7]	0.18
Weight, kgs, Median [IQR]	15 [10-28]	18 [11-33]	0.07
Prematurity, n (%)	21 (22)	22 (19)	0.62
Term of birth if prematurity, weeks of amenorrhea, Median([IQR]	33 [30-34]	31.5 [29-35]	0.75
History of atopic disease			
Familial	n = 84	n = 98	
Asthma, n (%)	47 (56)	54 (55)	0.91
Atopy other than asthma, n (%)	17 (20)	20 (20)	0.98
Existence of an allergen found, n (%)	19 (25) n = 76	20 (21) n = 97	0.49
Personal	n = 94	n = 114	
Asthma, n (%)	77 (82)	98 (86)	0.43
Atopy other than asthma, n (%)	16 (17)	25 (22)	0.36
Existence of an allergen found, n (%)	18 (19)	31 (27)	0.16
Personal characteristics of asthma	n = 77	n = 98	
Age at diagnosis, months, Median [IQR]	13.3 [6.9-33.5] n = 38	23.4 [7.7-76.1] n = 42	0.23
Type of asthma	n = 39	n = 82	0.66
Infectious	30 (77)	63 (77)	
Allergic	4 (10)	12 (15)	
Mixed	5 (13)	7 (8)	
History of hospitalization for exacerbation, n (%)	41 (55) n = 74	55 (59) n = 94	0.69
History of PICU hospitalization for exacerbation, n (%)	11 (14) n = 76	15 (15) n = 98	0.88
Frequency of SABAs use	n = 12	n = 28	**0.04**
Daily	0/12 (0)	9/28 (32)	
Weekly	2/12 (17)	3/28 (11)	
Monthly	7/12 (58)	13/28 (46)	
Yearly	3/12 (25)	1/28 (4)	
> Yearly	0/12 (0)	2/28 (7)	
Exacerbation protocol available at home, n (%)	10 (27) n = 37	52 (63) n = 83	**< 0.001**
Background treatment, n (%)	38 (51) n = 75	67 (68) n = 98	**0.02**
Chronic respiratory failure, n (%)	3 (3)	4 (4)	0.9
Ventilator support at home, n (%)	0/3 (0)	2/4 (50)	0.43

kgs: kilograms
PICU: Pediatric Intensive Care Unit
SABAs: Short-Acting β(2)Agonists

Table 2 | Clinical and paraclinical characteristics of children at PICU admission

	IV β2 + Inhaled β2 *(IV/inhβ2+)* **n = 95**	**IV β2** *(IVβ2+)* **n = 114**	***p*-value**
Severity scores			
PIM 2, Median [IQR]	1.25 [0.5-3] n = 80	1.1 [0.4-1.7] n = 63	0.47
PIM 3, Median [IQR]	0.3 [0.2-0.6] n = 15	0.23 [0.18-0.57] n = 70	0.51
PELOD 2, Median [IQR]	0.1 [0.1-0.2] n = 17	0 [0-3] n = 81	0.71
Constants at admission	n = 95	n = 113	
Heart rate, bpm, +/- SD	168.4 +/- 26.6	157.1 +/- 25.9	**0.002**
Respiratory rate, rpm, +/- SD	38.8 +/- 13.8	37.8 +/- 16.3	0.63
Systolic blood pressure, mmHg, +/- SD	116.2 +/- 17.9	111.8 +/- 14.5	0.06
Diastolic blood pressure, mmHg, +/- SD	64.5 +/- 19.1	71.5 +/- 15.2	**0.004**
Mean blood pressure, mmHg, +/- SD	78.9 +/- 17.8	85.02 +/- 13.9	**0.01**
Temperature, °C, Median [IQR]	37.2 [36.7-37.9]	37.4 [36.8-37.8]	0.75
Blood gas at admission (arterial, venous, capillary)			
pCO2, mmHg, Median [IQR]	37 [32-46]	44 [36-59]	**0.001**
HCO3, mmol/l, Median [IQR]	21.3 [12-36] n = 94	22 [5.2-34.6] n = 114	0.08
Lactate, mmol/l, Median [IQR]	2.4 [0.8-9.6] n = 91	2.5 [0.52-18.2] n = 82	0.63
Potassium, mmol/l, Median [IQR]	4.4 [3.7-5.1] n = 92	3.6 [3-4.3] n = 75	< **0.001**
Pulmonary radiography	n = 94	n = 111	
Abnormality, n (%)	87 (93)	110 (99)	**0.03**
Thoracic distension	85/87 (98)	85/110 (77)	< **0.001**
Atelectasis	5/87 (6)	11/110 (10)	0.28
Pneumopathy	21/87 (24)	15/110 (14)	0.06
Bilateral alveolar-interstitial opacities	18/87 (21)	13/110 (12)	0.09
Pneumothorax / Pneumomediastinum	1/87 (1)	6/110 (6)	0.14

PIM: Pediatric Index of Mortality
PELOD: Pediatric Logistic Organ Dysfunction
bpm: beats per minute
rpm: respiration per minute
SD: standard deviation
pCO2: partial pressure of CO2

Table 3 | Medical support of children at PICU admission

	IV β2 + Inhaled β2 *(IV/inhβ2+)* n = 95	IV β2 *(IVβ2+)* n = 114	*p*-value
Pharmacological support			
Other nebulization(s), n (%)	58 (61) n = 95	87 (77) n = 113	**0.01**
Ipratropium	50/58 (86)	86/87 (99)	**0.003**
Inhaled corticoids	11/58 (19)	10/87 (12)	0.21
Terbutaline	9/58 (16)	5/87 (6)	0.05
Adrenaline	8/58 (14)	4/87 (5)	0.07
Systemic corticosteroids, n (%)	89 (94) n = 95	108 (96) n = 113	0.54
$MgSO_4$, n (%)	20 (21) n = 95	44 (39) n = 113	**0.005**
Hemodynamic support			
Vascular filling, n (%)	22 (23)	18 (16)	0.18
Amines, n (%)	4 (4)	1 (1)	0.18
Norepinephrine	1/4 (25)	0/1 (0)	1.0
Epinephrine	4/4 (100)	1/1 (100)	-
Anti-infectious support			
Antibiotic treatment, n (%)	27 (28)	24 (21)	0.22
Respiratory support			
Oxygen dependency, n (%)	29 (100) n = 29	n = 39 (98) n = 40	1.0
FiO2, %, Median [IQR]	80 [52-100]	55 [43-85]	0.32
HFNC therapy, n (%)	10 (11)	25 (22)	**0.03**
Non -invasive ventilation, n (%)	6 (6)	1 (1)	**0.03**
CPAP	1 (17)	0 (0)	1.0
BiPAP	5 (83)	1 (100)	
Invasive ventilation	13 (14)	14 (12)	**0.03**

HFNC: High Flow Nasal Cannula
CPAP: Continuous Positive Airway Pressure
BiPAP: Bi-level Positive Airway Pressure

Table 4 | Second line pharmacological support of children during PICU stay

Pharmacological support	**IV β2 + Inhaled β2** ***(IV/inhβ2+)*** **n = 95**	**IV β2** ***(IVβ2+)*** **n = 114**	***p*-value**
Ipratropium, n (%)	81 (85)	61 (54)	**< 0.001**
Duration, hours, Median [IQR]	48.3 [10.5-57.4] n = 46	19.5 [9.63-62.4] n = 24	0.07
Continued on discharge, n (%)	33 (42) n = 78	37 (62) n = 60	**0.02**
Inhaled corticoids, n (%)	71 (75)	18 (16)	**< 0.001**
Duration, hours, Median [IQR]	4 n = 1	0.38 [0.33-12.7] n = 5	**-**
Continued on discharge, n (%)	69 (99) n = 70	13 (72) n = 18	**0.001**
Systemic corticosteroids, n (%)	95 (100)	113 (99)	1.0
Duration, hours, Median [IQR]	92.5 [43.5-141.2] n = 15	186.4 [173-333.1] n = 8	**0.01**
Maximum dosage, mg/kg/day, Median [IQR]	2 [2-4] n = 94	2 [2-4] n = 113	0.77
Continued on discharge, n (%)	79 (89) n = 91	107 (97) n = 111	**0.01**
$MgSO_4$, n (%)	14 (15)	16 (14)	0.89

MgSO4: Magnesium Sulfate

Table 5 | Occurrence of complications during PICU stay	**IV β2 + Inhaled β2** ***(IV/inhβ2+)*** **n = 95**	**IV β2** ***(IVβ2+)*** **n = 114**	***p*-value**
Necessity of respiratory support, n (%)	94 (99)	112 (98)	1.0
HFNC therapy, n (%)	39 (41)	79 (71)	**< 0.001**
Duration, hours, Median [IQR]	40.1 [29.8-51]	25.5 [15.7-43]	**0.01**
Maximal FiO2, %, Median [IQR]	45 [30-60]	40.1 [29.8-51]	0.05
Non invasive ventilation, n (%)	18 (19)	12 (11)	0.09
CPAP	1 (6)	1 (9)	1.0
BiPAP	16 (94)	6 (55)	**0.02**
Duration, hours, Median [IQR]	28.6 [6.3-70] n = 17	12 [5-19.8] n = 10	0.34
Maximal PEEP, cmH20, Median (IQR)	6 [5-6] n = 15	5 [3-7] n = 10	0.74
Maximal FiO2, %, Median [IQR]	77 [60-100] n = 15	68 [60-100] n = 11	0.69
Invasive ventilation, n (%)	22 (23)	24 (21)	0.74
Duration, hours, Median [IQR]	3.9 [1.73-6.23]	1.1 [0.59-7.42]	0.10
Maximal PEEP, cmH20, Median [IQR]	5 [4-6] n = 21	5 [3.5-6.5] n = 23	1.0
Maximal FiO2, %, Median [IQR]	100 [80-100] n = 22	98 [60-100] n = 23	0.23
Ventilation support at discharge, n (%)	31 (34) n = 91	26 (24) n = 110	0.10
Necessity of hemodynamic support			
Vascular filling, n (%)	31 (33)	23 (20)	**0.04**
Number	2 [1-2]	2 [1-2]	0.51
Amines, n (%)	9 (9)	7 (6)	0.37
Norepinephrine	6/9 (67)	6/7 (86)	0.59
Epinephrine	2/9 (22)	2/7 (29)	1.0
Dobutamine	0/9 (0)	0/7 (0)	-
Dopamine	0/9 (0)	0/7 (0)	-
Milrinone	3/9 (33)	1/7 (14)	0.59
Duration, hours, Median (IQR)	25.3 [20-68] n = 7	23.7 [15.3-46] n = 6	0.72
ECMO, n (%)	1 (1)	2 (2)	1.0
Other, n (%)	9 (9)	10 (9)	0.86
Infectious complications			
Respiratory superinfection, n (%)	43 (45)	47 (41)	0.56
Duration of antibiotic treatment, days, Median [IQR]	2.2 [0.88-4.71] n = 10	4.6 [3.3-9.4] n =12	0.052
Secondary sepsis, n (%)	2 (2)	3 (3)	1.0
Miscellaneous			
Need for fasting, n (%)	94 (99)	114 (100)	-
Duration of fasting, hours, Median [IQR]	36 [24-48] n = 88	23.1 [12.7-46.3] n = 103	**< 0.001**

HFNC: High-Flow Nasal Cannula
CPAP: Continuous Positive Airway Pressure
BiPAP: Bi-level Positive Airway Pressure
PEP: Positive End-Expiratory Pressure
ECMO: ExtraCorporeal Membrane Oxygenation

Table 6 | Occurrence of adverse events related to β2-mimetics

	IV β2 + Inhaled β2 *(IV/inhβ2+)* n = 95	IV β2 *(IVβ2+)* n = 114	*p*-value
Occurrence of adverse event, n (%)	95 (100)	114 (100)	**-**
Tachycardia, n (%)	93 (98)	112 (98)	1.0
Duration, hours, Median [IQR]	47.2 [30.5-72.6] n = 86	42.1 [28.7-56.3] n = 90	0.35
Hypokalemia, n (%)	36 (38)	57 (50)	0.08
Minimum value, mmol/l, Median [IQR]	3.1 [2.9-3.2] n = 36	3 [2.8-3.2] n = 36	0.13
Clinical symptoms of severity	0 (0)	0 (0)	**-**
Necessity of specific management	26 (72)	24 (42)	**0.005**
Hyperlactatemia, n (%)	62 (65)	69 (61)	0.48
Duration, hours, Median [IQR]	14 [9-26] n = 59	9.8 [3.3-16.8] n = 67	**0.001**
Maximum value, mmol/l, Median [IQR]	4.85 [3.2-5.9]	4 [2.8-6.6]	0.47
Hyperglycemia, n (%)	88 (93)	95 (84)	0.06
Maximum value, mmol/l, Median [IQR]	14.8 [11.9-17.8]	14.9 [12.7-17.4]	0.71
Insulin therapy	8 (9)	2 (2)	0.05

FIGURES

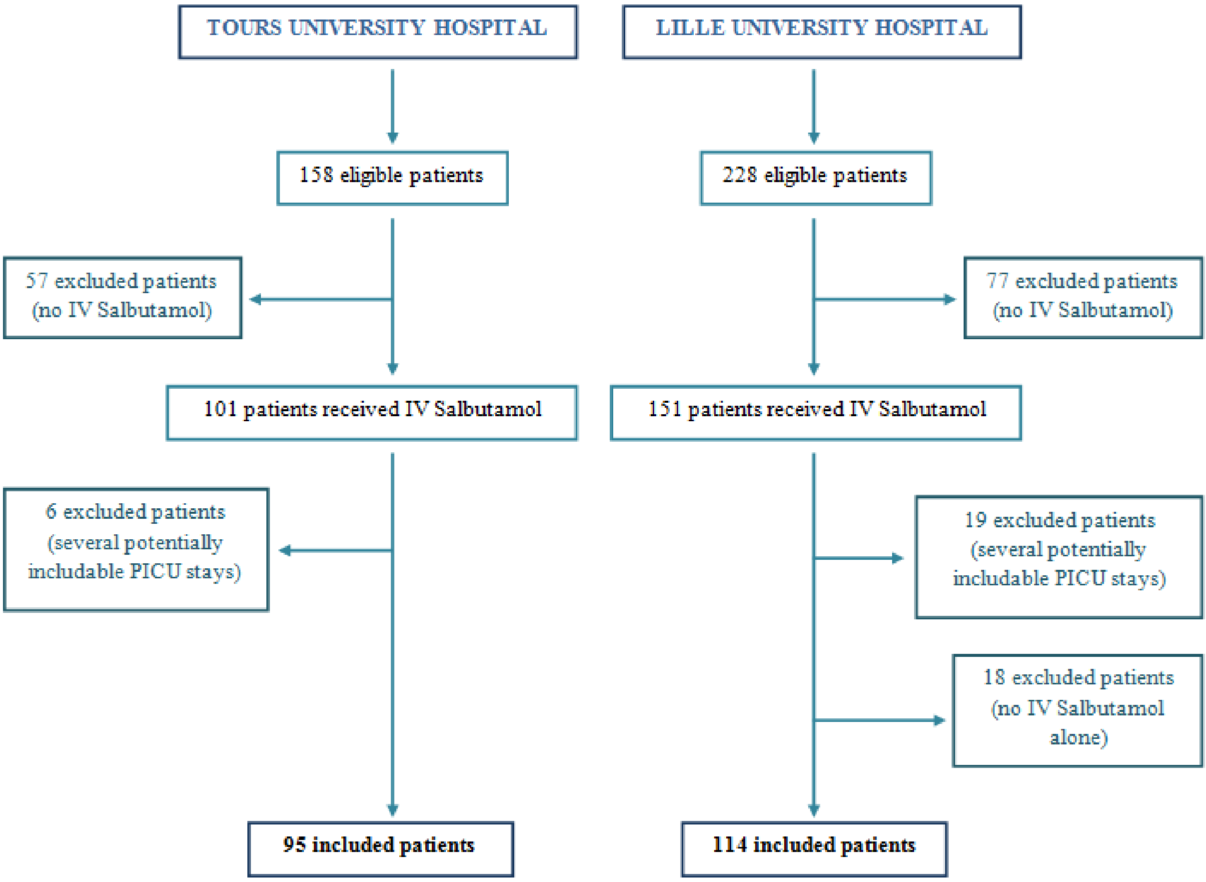

Figure 1 | Flow chart of the study
(eligible patients = patients selected from computer coding: "acute severe asthma")

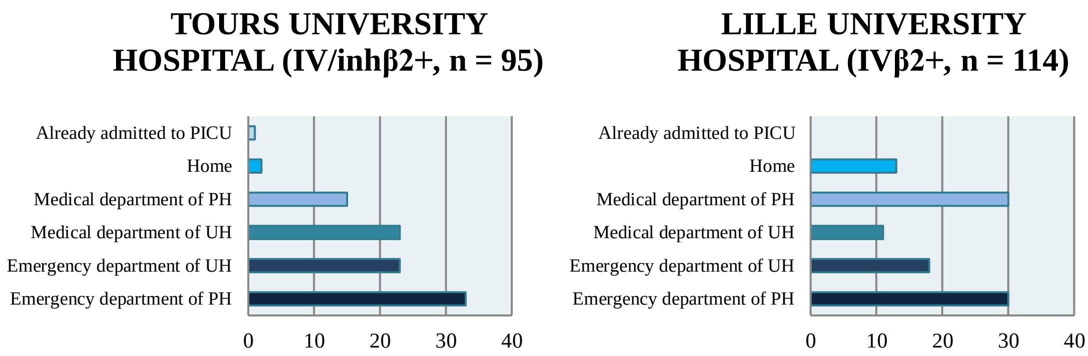

Figure 2 | Original department before transfer to PICU (%) (***p*<0.001**)
(PH: Peripheral Hospital; UH: University Hospital)

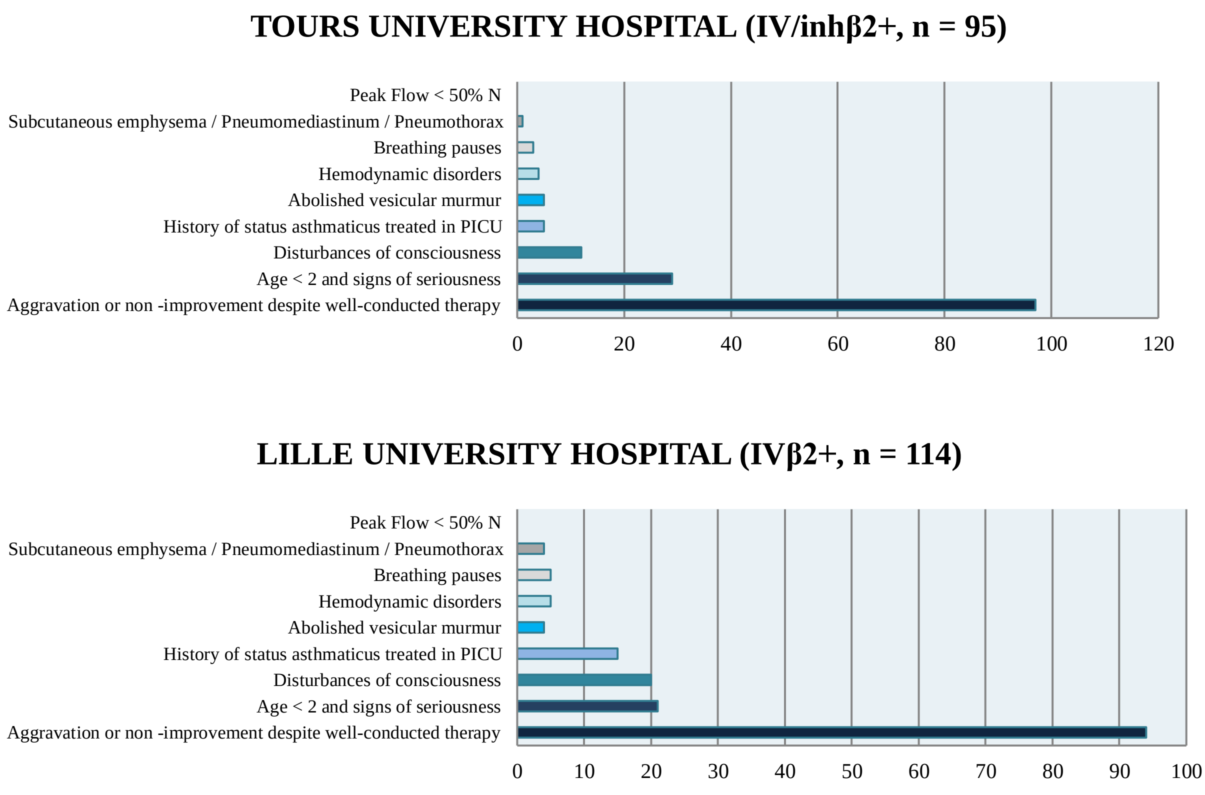

Figure 3 | Reasons for transfer to PICU (%)
(10% of children in the first group had > 2 reasons of transfer, versus 14% in the second group; p=0.325)

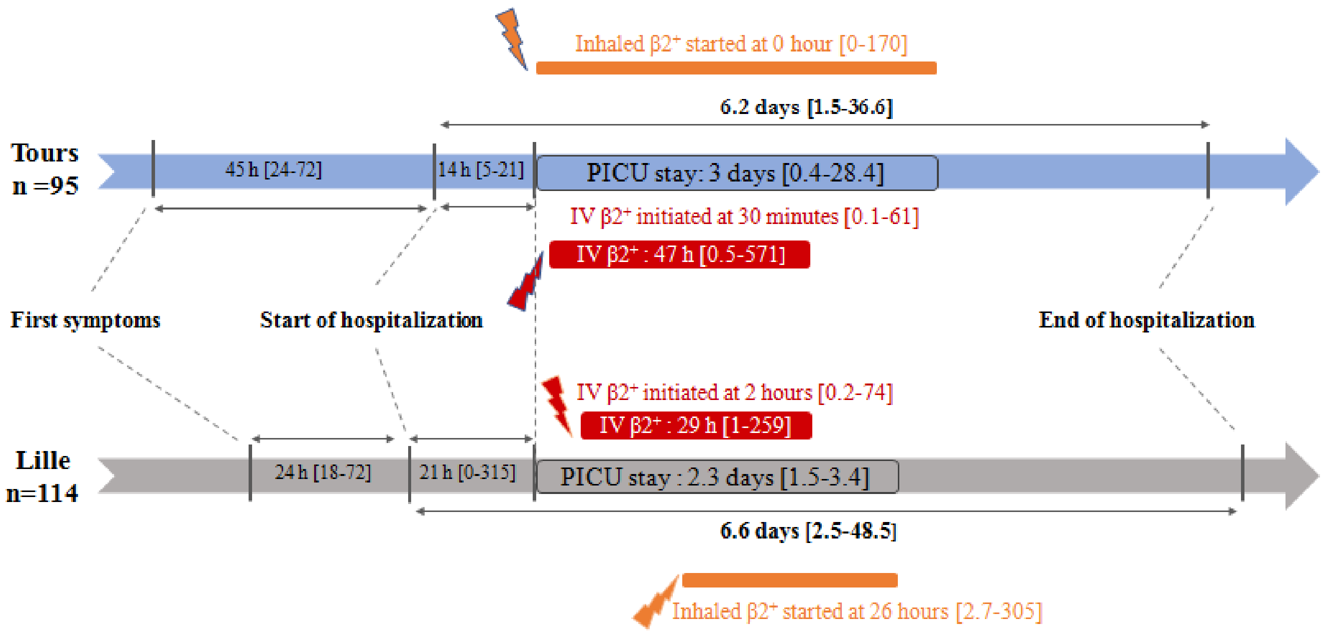

Figure 4 | Time to care, treatment and length of stay

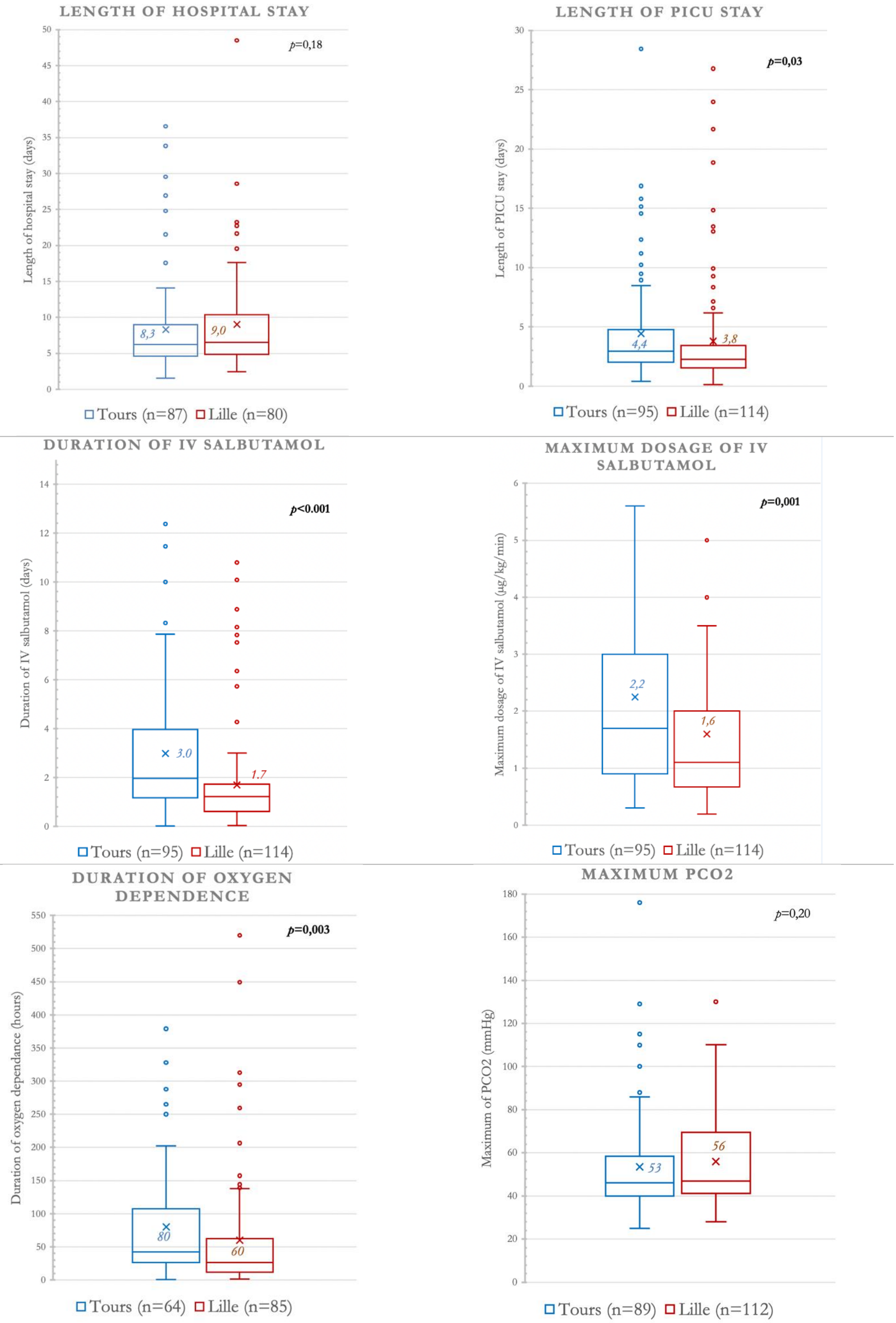

Figure 5 | Boxplots

Figure 6 | Supplementary file 1 - Information note to patients and families available at Tours University hospital

" La Recherche

est l'une des trois missions du CHRU "

INFORMATION AUX PATIENTS

Utilisation des données de santé pour la recherche et l'évaluation

Les données de votre dossier médical (ou de votre enfant) recueillies dans le cadre du soin peuvent être amenées à être réutilisées à des fins de recherche et d'évaluation, notamment via le centre de données cliniques du CHRU de TOURS, en collaboration avec les CHU du Grand Ouest. Ce dispositif informatisé, permet le traitement de vos données médicales dans le respect des règles éthiques, juridiques et déontologiques. Vos données pourront être croisées avec celles d'autres sources, telles que le système national des données de santé de l'Assurance-Maladie. Dans tous les cas, seules des personnes soumises au secret professionnel peuvent accéder à vos données, sous la responsabilité d'un médecin de l'établissement.

Conformément aux dispositions de la loi « Informatique et Libertés » (loi du 6 janvier 1978 modifiée*) et du RGPD**, toute recherche sur les données vous concernant sera conduite conformément aux dispositions législatives et règlementaires en vigueur.

Les analyses sont toujours réalisées dans le respect des règles de confidentialité sur des données codées sans mention des noms et prénoms et les résultats sont produits sous une forme agrégée qui ne permet en aucun cas de vous identifier. Il est également possible que vous soyez recontacté par le service qui vous a pris en charge pour vous proposer de participer à une nouvelle recherche.

Dans tous les cas (conformément à la loi Informatique et Libertés révisée et au RGPD), vous disposez d'un droit d'accès, de rectification, de portabilité et de limitation du traitement des données figurant dans votre dossier. Vous pouvez à tout moment vous opposer à leur réutilisation pour une ou plusieurs recherches, ou la totalité (www.chu-tours.fr/), pour autant que leur traitement ne réponde pas à une obligation légale, sans avoir à justifier votre refus. L'exercice de votre droit d'opposition sera sans conséquence sur votre prise en charge ou la qualité de votre relation avec les équipes médicales et soignantes. Vous pouvez également vous opposer à être recontacté pour participer à une nouvelle recherche. Enfin, vous avez le droit d'introduire une réclamation auprès de la CNIL.

** Loi Informatique et Liberté n° 78-17 du 6 janvier 1978 modifiée par la Loi 2018 -493 du 20Juin 2018 : relative à l'informatique, aux fichiers et aux libertés (conformément à la Directive 95/46 CE relative à la protection des données personnelles)*
*** RGPD : Règlement (UE) 2016/679 du Parlement européen et du Conseil du 27 avril 2016 (RGPD) ,relatif à la protection des personnes physiques à l'égard du traitement des données à caractère personnel et à la libre circulation de ces données.*

Pour exercer vos droits, à tout moment, vous pouvez contacter le délégué à la protection des données (DPO) du CHRU de TOURS, e-mail : dpo@chu-tours.fr

CHRU
HÔPITAUX DE TOURS

Table 7 | Supplementary file 2 - Pediatric Respiratory Assessment Measure (PRAM)

PRAM (Pediatric Respiratory Assessment Measure)				
	Score	**Score**	**Score**	**Score**
Signs	**0**	**1**	**2**	**3**
Suprasternal retractions	Absent		Present	
Scalene muscle contractions	Absent		Present	
Air entry	Normal	Decreased at bases	Widespread decrease	
Wheezing	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
Oxygen Saturation	≥95%	92-94%	<92%	

If asymmetric findings (air entry and wheezing) between right and left lungs, rate the more severe side

Vu, le Directeur de Thèse

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

SROUR Maya

42 Pages - 6 Tableaux – 5 Figures

<u>Résumé</u> :

<u>Introduction</u>: Devant des modalités d'utilisation des β2-mimétiques intraveineux (IV) encore insuffisamment étudiées dans le traitement de seconde ligne de l'asthme aigu grave de l'enfant, l'objectif principal de cette étude était de comparer l'efficacité de la poursuite ou non du salbutamol inhalé après son introduction par voie IV dans la prise en charge de seconde ligne de l'état de mal asthmatique de l'enfant.

<u>Méthodes</u>: Une étude rétrospective bicentrique a été conduite chez des enfants âgés de 28 jours à 18 ans avec un diagnostic d'asthme aigu grave admis entre 2010 et 2021 dans les unités pédiatriques de soins intensifs (UPSI) du CHU de Tours et de Lille. Les caractéristiques démographiques, de la maladie asthmatique, les données relatives aux séjours en UPSI (ex : supports ventilatoires et hémodynamiques, durées de séjour, évènements indésirables associés aux β2-mimétiques, suivi post-hospitalisation) ont notamment été recueillies à partir des dossiers informatisés des patients. Pour répondre à l'objectif principal, les critères d'évaluation étaient les suivants : durées d'hospitalisation et de séjour en UPSI, caractéristiques de l'utilisation du salbutamol IV (durée et posologie maximale), durée d'oxygénodépendance et capnie maximale.

<u>Résultats</u>: Un total de 95 patients a été inclus dans le groupe associant le salbutamol inhalé et IV (IV/inhβ2+ **-** CHU de Tours) et de 114 patients dans le groupe utilisant le salbutamol IV seul (IVβ2+ **-** CHU de Lille) avec un âge médian de 4 ans et 4,5 ans. Les deux groupes étaient comparables en termes de caractéristiques démographiques et cliniques, de motif de transfert en UPSI et de gravité à l'admission. La durée médiane du séjour en UPSI était de 2,3 jours dans le groupe IVβ2+ contre 3 jours dans le groupe IV/inhβ2+ (p=0,003). Le traitement par salbutamol IV était utilisé pendant une durée significativement plus courte lorsqu'il était utilisé seul avec une médiane à 29,4 heures contre 47,4 heures dans le groupe IV/inhβ2+ (p<0.001), et à une posologie maximale significativement plus faible, de respectivement 1,1µg/kg/min contre 1,7µg/kg/min (p=0,001). La durée médiane d'oxygénodépendance était de 26 heures dans le groupe IVβ2+ contre 42,2 heures dans celui IV/inhβ2+ (p=0,003). Il n'y avait pas de différence significative entre les deux groupes concernant la durée totale d'hospitalisation et la capnie maximale.

<u>Conclusion</u>: Cette étude semble montrer un bénéfice à l'utilisation du salbutamol IV seul pour la prise en charge de deuxième ligne de l'asthme aigu grave de l'enfant. Des études complémentaires sur des échantillons plus importants et utilisant des critères d'évaluation standardisés restent néanmoins nécessaires pour statuer quant à l'intérêt thérapeutique de cette stratégie.

<u>**Mots clés**</u>**:** Asthme aigu grave ; Beta2-mimétiques ; Salbutamol ; Nébulisation ; Intraveineux ; Unité pédiatrique de soins intensifs ; Ventilation ; Hémodynamique ; Sécurité.

<u>**Jury :**</u>

Président du Jury :	Professeur François LABARTHE
<u>Directeur de thèse</u> :	<u>Docteur Charlotte IDIER</u>
Membres du Jury :	Professeur Stéphane DAUGER
	Professeur Antoine GUILLON
	Docteur Julie CHANTREUIL
	Docteur Annie-Laure SUC
	Docteur Isabelle GIBERTINI

Date de soutenance : 04/10/2021