



**HAL**  
open science

# Association between surgical factors and severe outcome in infants with surgical necrotizing enterocolitis: a retrospective study in a tertiary neonatal intensive care unit

Anouck Granon

## ► To cite this version:

Anouck Granon. Association between surgical factors and severe outcome in infants with surgical necrotizing enterocolitis: a retrospective study in a tertiary neonatal intensive care unit. Human health and pathology. 2023. dumas-04259464

**HAL Id: dumas-04259464**

**<https://dumas.ccsd.cnrs.fr/dumas-04259464v1>**

Submitted on 26 Oct 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance.

La propriété intellectuelle du document reste entièrement celle du ou des auteurs. Les utilisateurs doivent respecter le droit d'auteur selon la législation en vigueur, et sont soumis aux règles habituelles du bon usage, comme pour les publications sur papier : respect des travaux originaux, citation, interdiction du pillage intellectuel, etc.

Il est mis à disposition de toute personne intéressée par l'intermédiaire de [l'archive ouverte DUMAS](#) (Dépôt Universitaire de Mémoires Après Soutenance).

Si vous désirez contacter son ou ses auteurs, nous vous invitons à consulter en ligne les annuaires de l'ordre des médecins, des pharmaciens et des sages-femmes.

Contact à la Bibliothèque universitaire de Médecine Pharmacie de Grenoble :

[bump-theses@univ-grenoble-alpes.fr](mailto:bump-theses@univ-grenoble-alpes.fr)

Année : 2023

**ASSOCIATION BETWEEN SURGICAL FACTORS AND SEVERE OUTCOME IN  
INFANTS WITH SURGICAL NECROTIZING ENTEROCOLITIS. A  
RETROSPECTIVE STUDY IN A TERTIARY NEONATAL INTENSIVE CARE UNIT**

THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

SPÉCIALITÉ : PÉDIATRIE

Par Mme Anouck GRANON

*[Données à caractère personnel]*

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 11/10/2023

DEVANT LE JURY COMPOSÉ DE :

Président du jury :

M. le Pr Thierry DEBILLON

Membres :

Mme le Dr Marie CHEVALLIER

Mme le Dr Julia DOUTAU (directrice de thèse)

M. le Dr Pierre-Yves RABATTU

Mme le Dr Nadège THOMASSIN

*L'UFR de Médecine de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.*

CORPS	NOM Prénom	DISCIPLINE UNIVERSITAIRE
PU-PH	ALBALADEJO Pierre	Anesthésiologie-réanimation et médecine péri-opératoire
PU-PH	ARVIEUX-BARTHÉLÉMY Catherine	Chirurgie viscérale et digestive
PU-PH	BAILLET Athan	Rhumatologie
PU-PH	BARONE-ROCHETTE Gilles	Cardiologie
PU-PH	BAYAT Sam	Physiologie
MCF Ass.MG	BENDAMENE Farouk	Médecine Générale
PU-PH	BENHAMOU Pierre-Yves	Endocrinologie, diabète et maladies métaboliques
PU-PH	BERGER François	Biologie cellulaire
MCU-PH	BÉTRY Cécile	Nutrition
MCU-PH	BIDART-COUTTON Marie	Biologie cellulaire
PU-PH	BIOULAC-ROGIER Stéphanie	Pédopsychiatrie ; addictologie
PU-PH	BLAISE Sophie	Chirurgie vasculaire ; médecine vasculaire
PR Ass. Méd.	BOILLLOT Bernard	Urologie
MCU-PH	BOISSET Sandrine	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	BONAZ Bruno	Gastroentérologie ; hépatologie
PU-PH	BONNETERRE Vincent	Médecine et santé au travail
PU-PH	BOREL Anne-Laure	Nutrition
PU-PH	BOSSON Jean-Luc	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	BOTTARI Serge	Biologie cellulaire
PR Ass.MG	BOUCHAUD Jacques	Médecine Générale
PU-PH	BOUGEROL Thierry	Psychiatrie d'adultes
PU-PH	BOUILLET Laurence	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie
MCU-PH	BOUSSAT Bastien	Épidémiologie, économie de la santé et prévention
PU-PH	BOUZAT Pierre	Anesthésiologie-réanimation et médecine péri-opératoire
PU-PH émérite	BRAMBILLA Christian	Pneumologie
PU-PH émérite	BRAMBILLA Elisabeth	Anatomie et cytologie pathologiques
MCU-PH	BRENIER-PINCHART Marie Pierre	Parasitologie et mycologie
PU-PH	BRICAULT Ivan	Radiologie et imagerie médicale
PU-PH	BRICHON Pierre-Yves	Chirurgie thoracique et cardiovasculaire
MCU-PH	BRIOT Raphaël	Thérapeutique-médecine de la douleur ; Addictologie
PU-PH émérite	CAHN Jean-Yves	Hématologie
PU-PH émérite	CARPENTIER Patrick	Chirurgie vasculaire, médecine vasculaire
PR Ass.MG	CARRILLO Yannick	Médecine Générale
MCU-PH	CASPAR Yvan	Bactériologie-virologie ; hygiène hospitalière
PU-PH émérite	CESBRON Jean-Yves	Immunologie
PU-PH	CHABARDÈS Stephan	Neurochirurgie
PU-PH	CHABRE Olivier	Endocrinologie, diabète et maladies métaboliques
PU-PH	CHAFFANJON Philippe	Anatomie
MCF Ass.MG	CHAMBOREDON Benoît	Médecine Générale

CORPS	NOM Prénom	DISCIPLINE UNIVERSITAIRE
PU-PH	CHARLES Julie	Dermato-vénéréologie
MCF Ass.MG	CHAUVET Marion	Médecine Générale
PU-PH	CHAVANON Olivier	Chirurgie thoracique et cardiovasculaire
MCU-PH	CHEVALLIER Marie	Pédiatrie
PU-PH	CHIQUET Christophe	Ophthalmologie
PU-PH	CHIRICA Mircea	Chirurgie viscérale et digestive
PU-PH	CINQUIN Philippe	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	CLAVARINO Giovanna	Immunologie
MCU-PH	CLIN CHERPEC Rita	Nutrition
PU-PH	COHEN Olivier	Histologie, embryologie et cytogénétique
PU-PH	COURVOISIER Aurélien	Chirurgie infantile
PU-PH	COUTTON Charles	Génétique
PU-PH	COUTURIER Pascal	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie
PU-PH	CRACOWSKI Jean-Luc	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
PU-PH	DEBATY Guillaume	Médecine d'Urgence
PU-PH	DEBILLON Thierry	Pédiatrie
PU-PH	DECAENS Thomas	Gastroentérologie ; hépatologie ; addictologie
PR Ass. Méd.	DEFAYE Pascal	Cardiologie
PU-PH	DEGANO Bruno	Pneumologie ; addictologie
PU-PH	DEMATTEIS Maurice	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
PU-PH émérite	DEMONGEOT Jacques	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	DERANSART Colin	Physiologie
PU-PH	DESCOTES Jean-Luc	Urologie
PU-PH	DETANTE Olivier	Neurologie
MCU-PH	DIETERICH Klaus	Génétique
MCU-PH	DOUTRELEAU Stéphane	Physiologie
PU-PH	DUMESTRE PÉRARD Chantal	Immunologie
PU-PH	ÉPAULARD Olivier	Maladies infectieuses ; Maladies tropicales
MCU-PH	EVAIN Jean-Noël	Anesthésiologie-réanimation et médecine périopératoire
MCU-PH	EYSSERIC Hélène	Médecine légale et droit de la santé
PU-PH émérite	FAGRET Daniel	Biophysique et médecine nucléaire
PU-PH	FAUCHERON Jean-Luc	Chirurgie viscérale et digestive
PU-PH	FAURE Julien	Biochimie et biologie moléculaire
PU-PH	FERRETTI Gilbert	Radiologie et imagerie médicale
PU-PH	FIARD Gaëlle	Urologie
PU-PH	FONTAINE Éric	Nutrition
PU-PH émérite	FRANÇOIS Patrice	Épidémiologie, économie de la santé et prévention
PR Ass. Méd.	FREY Gil	Chirurgie thoracique et cardiovasculaire
MCU-MG	GABOREAU Yoann	Médecine Générale
PU-PH	GARBAN Frédéric	Hématologie ; Transfusion
PU-PH	GAUDIN Philippe	Rhumatologie
MCU-PH	GAUTIER-VEYRET Elodie	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
PU-PH	GAVAZZI Gaétan	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie

CORPS	NOM Prénom	DISCIPLINE UNIVERSITAIRE
PU-PH	GAY Emmanuel	Neurochirurgie
MCU-PH	GIAI Joris	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	GILLOIS Pierre	Biostatistiques, informatique médicale et technologies de communication
PU-PH	GIOT Jean-Philippe	Chirurgie plastique, reconstructrice et esthétique ; Brûlologie
MCU-PH	GRAND Sylvie	Radiologie et imagerie médicale
PU-PH émérite	GRIFFET Jacques	Chirurgie infantile
PU-PH	HAINAUT Pierre	Biochimie et biologie moléculaire
PU-PH	HENNEBICQ Sylviane	Biologie et médecine du développement et de la reproduction ; gynécologie médicale
PU-PH	HOFFMANN Pascale	Gynécologie-obstétrique ; gynécologie médicale
PU-PH émérite	HOMMEL Marc	Neurologie
PU-MG	IMBERT Patrick	Médecine Générale
PU-PH émérite	JOUK Pierre-Simon	Génétique
PU-PH	KAHANE Philippe	Physiologie
PU-PH	KASTLER Adrian	Radiologie et imagerie médicale
MCU-PH	KHERRAF Zine-Eddine	Biologie et médecine du développement et de la reproduction ; gynécologie médicale
PU-PH	KRAINIK Alexandre	Radiologie et imagerie médicale
PU-PH	LABARÈRE José	Épidémiologie, économie de la santé et prévention
PU-PH	LABLANCHE (CORNALI) Sandrine	Endocrinologie, diabète et maladies métaboliques
PU-PH	LANDELLE Caroline	Bactériologie – virologie ; Hygiène hospitalière
PU-PH	LANTUEJOL Sylvie	Anatomie et cytologie pathologiques
PR Ass. Méd.	LARAMAS Mathieu	Cancérologie ; radiothérapie
MCU-PH	LARDY Bernard	Biochimie et biologie moléculaire
PU-PH	LAURENT-COSTENTIN Charlotte	Gastroentérologie ; hépatologie ; addictologie
MCU-PH	LE GOUËLLEC LE PISSART Audrey	Biochimie et biologie moléculaire
MCU-PH	LE MARÉCHAL Marion	Maladies infectieuses ; maladies tropicales
PU-PH	LECCIA Marie-Thérèse	Dermato-vénérologie
PR Ass.MG	LEDOUX Jean-Nicolas	Médecine Générale
PU-PH émérite	LÉTOUBLON Christian	Chirurgie viscérale et digestive
PU-PH émérite	LÉVY Patrick	Physiologie
PU-PH	LONG Jean-Alexandre	Urologie
MCU-PH	LUPO Julien	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	MAÎTRE Anne	Médecine et santé au travail
MCU-PH	MARLU Raphaël	Hématologie ; Transfusion
PR Ass. Méd.	MATHIEU Nicolas	Gastroentérologie ; hépatologie ; addictologie
MCU-PH	MAUBON Danièle	Parasitologie et mycologie
PU-PH	MAURIN Max	Bactériologie-virologie ; Hygiène hospitalière
MCU-PH	MC LEER Anne	Histologie, embryologie et cytogénétique
MCU-PH	MEONI Sara	Neurologie
PR Ass. Méd.	MICHY Thierry	Gynécologie-obstétrique
MCU-PH	MONDET Julie	Histologie, embryologie et cytogénétique
PU-PH	MORAND Patrice	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	MOREAU-GAUDRY Alexandre	Biostatistiques, informatique médicale et technologies de communication
PU-PH	MORO Elena	Neurologie

CORPS	NOM Prénom	DISCIPLINE UNIVERSITAIRE
PU-PH	MORO-SIBILOT Denis	Pneumologie ; addictologie
MCU-PH	MORTAMET Guillaume	Pédiatrie
PU-PH émérite	MOUSSEAU Mireille	Cancérologie ; radiothérapie
PU-PH émérite	MOUTET François	Chirurgie plastique, reconstructrice et esthétique ; brûlologie
PR Ass.MG	ODDOU Christel	Médecine Générale
PR Ass. Méd.	ORMEZANO Olivier	Cardiologie
MCU-PH	PACLET Marie-Hélène	Biochimie et biologie moléculaire
PU-PH	PAILHÉ Régis	Chirurgie orthopédique et traumatologie
PU-PH	PALOMBI Olivier	Anatomie
PU-PH	PARK Sophie	Hématologie ; Transfusion
PR Ass.MG	PAUMIER-DESBRIÈRES Françoise	Médecine Générale
PU-PH	PAYEN DE LA GARANDERIE Jean-François	Anesthésiologie-réanimation et médecine péri-opératoire
MCU-PH	PAYSANT François	Médecine légale et droit de la santé
MCU-PH	PELLETIER Laurent	Biologie cellulaire
PU-PH	PELLOUX Hervé	Parasitologie et mycologie
PU-PH	PÉPIN Jean-Louis	Physiologie
PU-PH	PÉRENNOU Dominique	Médecine physique et de réadaptation
PAST	PICARD Julien	Anesthésiologie-réanimation et médecine péri-opératoire
PU-PH	PERNOD Gilles	Chirurgie vasculaire ; Médecine vasculaire
MCF	PINSAULT Nicolas	Sciences de la rééducation et de réadaptation
PU-PH	PIOLAT Christian	Chirurgie infantile
PU-PH émérite	PISON Christophe	Pneumologie ; Addictologie
PU-PH	PLANTAZ Dominique	Pédiatrie
PU-PH	POIGNARD Pascal	Bactériologie-virologie ; Hygiène hospitalière
PU-PH émérite	POLACK Benoît	Hématologie ; Transfusion
PU-PH	POLOSAN Mircea	Psychiatrie d'adultes ; Addictologie
PU-PH émérite	RAMBEAUD Jean-Jacques	Urologie
PU-PH	RAY Pierre	Biologie et médecine du développement et de la reproduction ; gynécologie médicale
PR Ass. Méd.	RECHE Fabian	Chirurgie viscérale et digestive
MCU-PH	RENDU John	Biochimie et biologie moléculaire
MCU-PH émérite	RIALLE Vincent	Biostatistiques, informatique médicale et technologies de communication
PU-PH	RIETHMULLER Didier	Gynécologie-obstétrique ; gynécologie médicale
PU-PH	RIGHINI Christian	Oto-rhino-laryngologie
PU-PH émérite	ROMANET Jean Paul	Ophtalmologie
PU-PH	ROSTAING Lionel	Néphrologie
PU-PH	ROUSTIT Matthieu	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
MCU-PH	ROUX-BUISSON Nathalie	Biochimie et biologie moléculaire
PR Ass.MG	ROYER DE VÉRICOURT Guillaume	Médecine Générale
PU-PH émérite	SARAGAGLIA Dominique	Chirurgie orthopédique et traumatologie
MCU-PH	SATRE Véronique	Génétique
PU-PH	SAUDOU Frédéric	Biologie cellulaire
PU-PH	SCHMERBER Sébastien	Oto-rhino-laryngologie
PU-PH	SCHWEBEL Carole	Médecine intensive-réanimation

CORPS	NOM Prénom	DISCIPLINE UNIVERSITAIRE
PU-PH	SCOLAN Virginie	Médecine légale et droit de la santé
PU-PH	SEIGNEURIN Arnaud	Épidémiologie, économie de la santé et prévention
PU-PH	SPEAR Rafaëlle	Chirurgie vasculaire ; médecine vasculaire
PU-PH émérite	STAHL Jean-Paul	Maladies infectieuses ; Maladies tropicales
PU-PH	STANKE Françoise	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
MCU-PH	STASIA Marie-José	Biochimie et biologie moléculaire
PU-PH	STURM Nathalie	Anatomie et cytologie pathologiques
PU-PH	TAMISIER Renaud	Physiologie
PU-PH	THEVENON Julien	Génétique
PU-PH	TOFFART Anne-Claire	Pneumologie ; Addictologie
PU-PH	TONETTI Jérôme	Chirurgie orthopédique et traumatologie
PU-PH	TOUSSAINT Bertrand	Biochimie et biologie moléculaire
PU-PH	VALMARY-DEGANO Séverine	Anatomie et cytologie pathologiques
PU-PH	VANZETTO Gérald	Cardiologie
PU-PH	VIGLINO Damien	Médecine d'urgence
PU-PH	VUILLEZ Jean-Philippe	Biophysique et médecine nucléaire
PU-PH	WEIL Georges	Épidémiologie, économie de la santé et prévention
PU-PH	ZAOUI Philippe	Néphrologie
PU-PH émérite	ZARSKI Jean-Pierre	Gastroentérologie ; hépatologie ; addictologie

PU-PH	Professeur des universités - Praticien hospitalier
MCU-PH	Maître de conférences des universités - Praticien hospitalier
PU-PH émérite*	Professeur des universités - Praticien hospitalier émérite
MCU-PH émérite*	Maître de conférences des universités - Praticien hospitalier émérite
PU-MG	Professeur des universités de médecine générale
MCU-MG	Maître de conférences des universités de médecine générale
MCF	Maître de conférences des universités
PR Ass. Med.	Professeur des universités associé (à mi-temps)
PR Ass. MG	Professeur des universités de médecine générale associé (à mi-temps)
MCF Ass.MG	Maître de conférences des universités de médecine générale associé (à mi-temps)
PAST	Professeur associé en service temporaire



**Contents**

**Acknowledgments..... 8**

**Abstract ..... 11**

**Résumé ..... 12**

**Abbreviations..... 14**

**I. Introduction ..... 15**

**II. Material and method ..... 16**

**III. Results..... 18**

**IV. Discussion..... 21**

**V. Conclusion ..... 25**

**VI. Figure and tables ..... 26**

*Figure 1: Flowchart ..... 26*

*Table 1: Neonatal characteristics..... 27*

*Table 2: Characteristics at time of necrotizing enterocolitis (NEC) diagnosis ..... 28*

*Table 3: Characteristics of NEC surgical management. .... 29*

*Table 3b: Characteristics of NEC surgical management continued..... 30*

*Table 4: Subgroup analysis: characteristics of infants according to surgical revision..... 31*

**VII. Supplemental tables ..... 32**

*Table 5: Subgroup analysis: characteristics of infants according to surgical indication. .... 32*

*Table 6: Surgical characteristics associated with death..... 33*

*Table 7: Ostomy level and outcome..... 34*

**VIII. References ..... 36**

## **Acknowledgments**

A **Monsieur le Pr Thierry DEBILLON** pour l'honneur que vous m'accordez d'avoir accepté de présider ce jury. Merci de votre soutien tout au long de ma formation.

A **Madame le Dr Marie CHEVALLIER** de participer à ce jury. Merci pour ta présence, ta bienveillance, ton encadrement pour la thèse.

A **Madame le Dr Julia DOUTAU** d'avoir dirigé ce travail et d'avoir accepté de participer à ce jury. Merci pour ta bienveillance et ta rigueur qui m'ont permis de mener ce travail à terme. Merci pour ta disponibilité même le week-end ou pendant les vacances.

A **Monsieur le Dr Pierre Yves RABATTU** d'avoir accepté de participer à ce jury. Merci de ta disponibilité et ta guidance.

A **Madame le Dr Nadège THOMASSIN** d'avoir accepté de faire partie de ce jury. Merci de m'avoir guidée sur la voie de la gastro-entérologie pédiatrique.

Merci à l'ensemble des professeurs, médecins, infirmiers et aides-soignants avec qui j'ai pu exercer au cours de mon internat pour leurs conseils et leur bienveillance.

A **l'équipe de pédiatrie polyvalente** pour m'avoir guidé dans mes premiers pas en tant qu'interne.

A **l'équipe de néonatalogie d'Annecy** pour m'avoir fait découvrir cette spécialité.

A **l'équipe de réanimation néonatale** de Grenoble pour m'avoir donné goût à la nutrition et à la réanimation même si c'est la nutrition qui l'a emportée.

A **l'équipe des urgences pédiatriques** de Grenoble pour l'autonomie que vous nous accordez tout en étant toujours disponibles pour répondre à nos questions.

A **l'équipe de Chambéry** pour sa bienveillance, pour m'avoir montré qu'il est possible de garder une activité polyvalente et que notre pratique peut évoluer en cours de route.

A **l'équipe de l'IHO** pour cet aperçu de l'oncologie pédiatrique.

A l'équipe d'hépatologie, gastro-entérologie et nutrition pédiatrique de Lyon pour m'avoir formée avec bienveillance et application. J'espère pouvoir continuer à exercer et progresser sur cette voie.

A ma famille :

A **mes parents** pour m'avoir soutenue tout au long de ma formation. Merci pour tous les petits plats préparés, les messages de soutien, les week-end de repos dans le diois, les escapades à cheval ou en montagne. Merci de m'avoir inculquée rigueur et application et de m'avoir permise de m'épanouir dans cette voie. Sans vous je n'en serais probablement pas là.

A ma **petite sœur** pour nos enguelades et nos fous rires. Pour nos échappées à cheval plus ou moins ardues. A **Arthur** qui a rejoint notre petite famille avec Tupac.

A mon **grand-père** toujours présent pour m'accueillir le temps d'un repas au milieu des révisions, pour avoir partagé sa passion pour sa terre natale et les jeux de cartes. A ma **grand-mère** que j'ai peu connue mais qui m'a probablement donnée l'envie de travailler à l'hôpital avec les enfants.

A **mes beaux-parents** pour leur générosité, pour ces cours de grimpe ou de ski de randonnée personnalisés et ces vacances en montagne.

A mes amis :

A **Zoé** que j'ai rencontré au lycée et avec qui j'ai partagé ma première année de médecine, fait mes premiers voyages entre amies.

A mes amis d'externat.

A **Sarah** pour son oreille attentive et sa gentillesse sans faille, toujours prête à accueillir et parfaite de compagne de révision ou de voyage. A **Chloé** pour ses fous rires et son don pour raconter les histoires, pour ces sorties inoubliables en montagne, ces voyages insolites. A **Laetitia** toujours disponible pour partager un repas ou un verre, DJ qui enflamme nos soirées. A **Duncan** et **Mégane** pour toutes ces soirées de nouvel an. A **Perrine** et **Hanna** pour votre assiduité et vos rappels à l'ordre quand nous étions trop dissipées lors des révisions. A **Dolly** pour son refus des conventions et sa liberté de pensées. A **Thomas** toujours disponible pour

une sortie à ski, ou pour aller boire une bière. A **Rémi** compagnon de liqueur et premier trentenaire du groupe.

A ceux rencontrés pendant l'internat :

A **Mélanie** binôme de réanimation néonatale, ce fut un plaisir de travailler avec toi, prête à récidiver quand tu veux ! A **Lucy** toujours une oreille à l'écoute, binôme de shopping ou de brunch mais aussi de potins. A **Camille** toujours calme et à l'écoute, tu es le roc de la promo. A **Caro et Jérémie** toujours le sourire, généreux. A **Charlotte, Thibaud, Géraldine et Lucile** même si nous n'avons pas eu l'occasion de travailler ensemble, parfaits compagnons de promo et de simu. A **Nour** et **Lauren** compagnon d'IHO et de restaurants, merci pour votre bonne humeur et tous ces partages gourmands. A **Gauthier** rencontré plus tard, nouveau compagnon de cordée, de bière, et de voyage.

Et enfin à **Johan**, compagnon de ski rencontré au début de l'internat devenu compagnon de cordée et compagnon de vie. Merci à toi d'être à mes côtés et de supporter mes coups de mou, de me rassurer quand je panique. Merci de m'avoir accompagnée tout au long de mon internat et d'être prêt à me suivre vers l'inconnue. Je t'aime.

## **Abstract**

Introduction: A quarter of neonates with necrotizing enterocolitis (NEC) undergo surgery. Surgical management has changed little and is difficult to assess, whereas comorbidities are increasingly often described and studied in the literature. The main objective of our study was to determine surgical factors associated with survival without parenteral feeding in newborns with NEC managed surgically, with comparison to the literature.

Material and methods: This retrospective cohort study was conducted in a tertiary neonatal surgery referral center for the period January 2010 to June 2022. All infants treated surgically for NEC were recruited. Exclusion criteria comprised NEC complicating preexisting digestive pathology, surgery for stenosis secondary to NEC treated medically, and isolated spontaneous intestinal perforation.

Results: Forty-one patients were included; 66% were under parenteral feeding at term or at death. Median gestational age was 30.0 weeks; median weight was 1,370 g. Primary drainage was implemented in 11 cases (27.5%) and primary ostomy in 26 (65.0%), with no difference between the two groups (survival free of parenteral feeding, and deceased or with continuing parenteral feeding). In the group of patients deceased or surviving with parental feeding at 41 weeks gestational age, 18 infants ( $p=0.026$ ) underwent revision surgery, 17 required proximal ostomy ( $p<0.001$ ), and 12 were operated on for hemodynamic shock ( $p=0.003$ ). The main study data were comparable to those in the literature, which shows wide variation.

Conclusion: Two-thirds of this cohort of NEC managed surgically in a tertiary neonatal intensive care unit presented adverse outcome: death or parenteral feeding continuing at term. These infants presented significantly more frequent proximal ostomy and surgical

revision. Surgery mainly consisted in resection of the necrotic bowel with ostomy. The review of the literature showed wide variation in practices. Larger-scale prospective research could detail surgical practices and outcome.

## **Résumé**

Introduction : Un quart des nouveau-nés atteints d'entérocolite ulcéro-nécrosante (ECUN) nécessitent une prise en charge chirurgicale. Les pratiques chirurgicales pour l'ECUN ont peu changé et sont difficiles à évaluer, alors que les comorbidités sont de plus en plus décrites et étudiées dans la littérature. L'objectif principal de notre étude était de décrire les caractéristiques chirurgicales associées à la survie sans parentérale des nouveau-nés atteints d'ECUN pris en charge chirurgicalement, avec une comparaison à la littérature.

Matériel et méthodes : cette cohorte rétrospective a été menée dans un centre tertiaire de référence pour la chirurgie néonatale de janvier 2010 à juin 2022. Tous les nourrissons traités chirurgicalement pour une ECUN ont été inclus. Les critères d'exclusion étaient les NEC compliquant des pathologies digestives préexistantes, la chirurgie pour sténose secondaire à une ECUN traitée médicalement et la perforation intestinale spontanée isolée.

Résultats : au total, 41 patients ont été inclus, 66% avaient besoin d'une parentérale à terme ou sont décédés. L'âge gestationnel médian était de 30,0 SA et le poids médian de 1370g. Le drainage primaire a concerné 11 (27,5 %) de la population, la stomie primaire 26 (65,0 %), sans différence entre les deux groupes. Dans le groupe décès ou survivant avec parentérale à 41 SA, 18 nourrissons ( $p=0,026$ ) ont nécessité une reprise chirurgicale, 17 nouveau-nés ont eu une stomie proximale ( $p<0,001$ ) et 12 ont été opérés pour un choc hémodynamique

( $p=0.003$ ). Par rapport à la littérature, les principales variables sont similaires, avec de grandes variations dans les données de la littérature.

Conclusion : dans cette cohorte de NEC traitées chirurgicalement dans un service de néonatalogie de niveau trois, les deux tiers de la population ont présenté une issue défavorable, un décès ou un besoin de nutrition parentérale à terme. Ces nourrissons ont présenté un nombre significativement plus élevé de stomies proximales et de reprises chirurgicales. La principale intervention chirurgicale a été la résection de l'intestin nécrosé avec stomie. La revue de la littérature associée à notre étude a montré une énorme variation des pratiques. Des recherches prospectives de plus grande envergure pourraient permettre de préciser la pratique chirurgicale globale et le devenir.

## Abbreviations

AC: antenatal corticosteroids

BPD: bronchopulmonary dysplasia

CC: central catheter

ECUN: entérocolite ulcéro-nécrosante

FMT: failed medical treatment

GA: gestational age

ICV: ileocecal valve

IVH: intraventricular hemorrhage

NEC: necrotizing enterocolitis

NICU: neonatal intensive care unit

PDA: persistent ductus arteriosus

PTR: preterm retinopathy

SB: small bowel

SGA: small for gestational age

wGA: weeks' gestational age



## I. Introduction

Necrotizing enterocolitis (NEC) is a serious pathology of prematurity, affecting 7-10% of preterm infants<sup>1,2</sup>. 13% of children with NEC die from their disease<sup>3</sup>. A quarter of neonates with NEC need surgical treatment; mortality rises to 30% in children requiring surgery<sup>3</sup>.

NEC is a severe inflammatory ischemic disease of the bowel leading to necrosis, and may be complicated by digestive perforation, sepsis, peritonitis or organ failure. Origin is multifactorial, associating altered microbiota, genetic polymorphism and digestive tract immaturity<sup>4,5</sup>. Suspicion is clinical, based on rectal bleeding, occlusive syndrome, inflammatory digestive placard, and hemodynamic or respiratory deterioration. Diagnosis is confirmed on abdomen radiology by signs of pneumatosis, aeroportia or pneumoperitoneum. Severity is assessed on Bell score<sup>6</sup>.

Therapeutic strategy has changed little over the years<sup>7</sup>. For non-severe NEC, management is medical, with fasting and antibiotics<sup>8</sup>. More severe NEC further requires primary or secondary surgery. Surgery is clearly indicated in case of pneumoperitoneum. Although widely approved, indications for and timing of surgery are still subjective in case of failed medical treatment<sup>9</sup>. Several strategies are available. Surgery usually consists in exploratory laparotomy, resection of the necrotic bowel, with one step restoration of continuity or, more frequently, stoma placement. If cardiorespiratory status does not allow surgery, peritoneal drainage alone is performed in first line<sup>7,10</sup>. Rates of postoperative comorbidity are 20-35%<sup>11</sup>. Medium-term comorbidities are also important, with dependence on parenteral nutrition in 10-40% of cases<sup>12,13</sup>, and digestive stenosis in 10-36%<sup>11,14,15</sup>. In the

longer term, neurodevelopmental comorbidities are important, particularly for children with surgically managed NEC<sup>16</sup>.

Overall, surgical practices for NEC have changed little and are difficult to assess <sup>14,17</sup>, whereas comorbidities are increasingly often described and studied in the literature. The main objective of our study was to determine surgical characteristics associated with survival without parenteral feeding in newborns with NEC managed surgically in a tertiary neonatal center, with comparison to literature.

## **II. Material and method**

### **Study design**

This single-center observational study was conducted in the University Hospital of Grenoble, France, a tertiary referral center for neonatal surgery, with a retrospective chart review for the period January 2010 to June 2022. All infants treated surgically for NEC and admitted to the neonatal intensive care unit (NICU) were recruited. Exclusion criteria comprised NEC complicating preexisting digestive pathology, NEC after 41 weeks' gestational age (wGA), surgery for stenosis secondary to NEC treated medically, or isolated spontaneous intestinal perforation. We crossed the databases of the surgical and neonatal registers. NEC was suspected on clinical and radiological features, and diagnosis was validated from surgical records, and by histopathology if available.

### **Primary endpoint**

The primary endpoint was composite: death or continuing parenteral feeding at 41wGA, as associated with severe outcome in previous studies <sup>18,19</sup>.

## Secondary endpoints

Secondary endpoints comprised comparison of the main results to the literature.

## Data collection

Data were collected from medical and surgical charts. Classical perinatal characteristics were recorded. Neonatal data comprised: hemodynamically significant patent ductus arteriosus (PDA), treated by paracetamol or ibuprofen; grade 3 or 4 bronchopulmonary dysplasia (BPD) according to Bancalari and Jobe<sup>20</sup>; central catheter (CC)-related infection, defined as clinical features associated to sepsis and positive hemoculture; and grade 3 or 4 intraventricular hemorrhage (IVH) according to the Papille classification<sup>21</sup>.

The main characteristics of primary surgery comprised surgical indication<sup>7</sup> with pneumoperitoneum diagnosed on X-ray, and failed maximal medical treatment, detailed as occlusive syndrome persisting despite optimal medical treatment<sup>22,23</sup>, hemodynamic shock due to NEC<sup>24</sup>, respiratory instability according to the clinician, or other indications. Several medical treatment failure indications could be associated. Other surgical data comprised: location (operating room or bedside), prior drainage or direct laparotomy, need for ostomy, and feasibility of closing the abdominal wall. Surgery timing was measured between first radiography at diagnosis and time of surgery. Organizational factors which could impact the surgery, such as transfer from another NICU, surgery during night shift, weekends or public holidays, were recorded<sup>25-27</sup>. Surgical revision included second-look surgery, revision after peritoneal drainage and revision after poor clinical and biological progression; the timing of revision surgery was also noted. In case of postoperative ostomy, an anatomical scale<sup>28</sup> was used to determine level: proximal jejunal, distal jejunal, proximal ileum, distal ileum, or colic.

The length of small bowel resected, and ileocecal valve conservation were recorded. Time (in days) to restored continuity was reported.

### **Statistical analysis**

Continuous variables were expressed as median and interquartile range, and were analyzed on Mann-Whitney test. Categorical variables were expressed as number and percentage, and were analyzed on Fisher exact test. P-values less than 0.05 were considered statistically significant. All analyses used Jamovi software, version 2.3.21.0.

### **Ethics**

This study was approved by the local institutional review board and was conducted in compliance with French MR004 regulations.

## **III. Results**

The analysis included 41 neonates presenting surgical NEC before 41 wGA between January 2010 and June 2022. (**Figure 1**). Maternal and perinatal characteristics are presented in **Table 1**. Median gestational age was 30.0 wGA, and median weight was 1,370 g. Infants surviving without parenteral feeding at term were less likely to have persistent ductus arteriosus ( $p=0.035$ ). Otherwise, there were no significant differences in perinatal data and neonatal comorbidities (**Table 1**). Nine of the 41 neonates (21.9%) died perioperatively or from NEC-related complications and 18 (43.9%) still needed parenteral feeding at 41 wGA. Overall, 27 neonates (65.8%) had adverse outcomes.

Characteristics at NEC diagnosis are compared in **Table 2**. In the two groups, survival free of parenteral feeding and deceased or with continuing parenteral feeding, median age at

diagnosis was respectively 14 and 16 days ( $p=0.934$ ), for a corrected age of 33.8 and 32.0 wGA ( $p=0.371$ ), with no significant difference. Radiographically, there were no significant differences, although with a trend for more frequent pneumoperitoneum in group survival free of parenteral feeding: 10 (71%) versus 11 (44%),  $p=0.100$ . There were no differences in inotrope support or respiratory support.

Concerning surgical management (**Table 3**), ages at surgery were also similar, 16 in group survival free of parenteral feeding and 17 days in group death or parenteral feeding ( $p = 0.978$ ) for an overall median of 34.4 wGA ( $p = 0.762$ ). Although neonates in group parenteral-free survival tended to be heavier, the difference was not significant: 1,875 g and 1,530 g ( $p=0.329$ ). No significant difference was observed for surgery timing: 48.0 hours in group parenteral-free survival, and 24.0 hours in group death or parenteral feeding ( $p=0.323$ ). Organizational factors such as patient transfer, surgery on nightshift or public holidays did not impact outcome. Neonates with surgery indicated for hemodynamic shock had more adverse outcome than those with pneumoperitoneum ( $p=0.003$ ). There were no significant differences for the other indications. Primary drainage was implemented for 11 neonates (27.5%), and primary ostomy for 26 (65.0%). Twenty-two neonates (53.7%) underwent revision surgery: 18 in group death or surviving with parental feeding at 41 wGA, (66.7%) versus 4 in group parenteral-free survival (28.6%) ( $p=0.026$ ). Proximal ostomy was associated with adverse outcome: 4 in group parenteral-free survival (14.3%) versus 17 in group death or parenteral feeding (77.3%) ( $p<0.001$ ). There were no significant differences in conservation of the ileocecal valve, or length of conserved bowel (with some missing data). Time to restoring continuity was respectively 66 and 69 days, with no significant difference ( $p=0.500$ ). Bowel

continuity was restored before term for only 29.0% of neonates: 5 (35.7%) in group parenteral-free survival and 4 (23.5%) in group death or parenteral feeding, with no significant difference ( $p=0.693$ ).

In the literature and in the present study, age in days of life at surgery was similar, but was older in terms of corrected age in the present study: 34 wGA versus 29-32wGA. In the literature, one study investigated surgery timing and transfer from a peripheral hospital<sup>18</sup>: surgery timing was similar to that in the present study, at 34.9 and 37.2 hours. The proportion of surgery for pneumoperitoneum, at around 50%, was similar to that reported in the literature<sup>1,18</sup>. The percentages of primary drainage, primary laparotomy and primary ostomy vary widely from one study to another<sup>1,14,15,18,29-31</sup>. The present rate of revision surgery was quite similar to that in the literature: 50%<sup>32,33</sup>. Continuity restoration was between 40.0 and 52.0 wGA in the literature<sup>34</sup>, it was sooner in term of days post ostomy in the present study, at 69 days versus 73-124 days<sup>28,32,34</sup>.

Regarding surgical revision (**Table 4**), infants who required revision were more immature (28.6 wGA versus 32.4 wGA;  $p=0.004$ ), and smaller ( $p=0.006$ ). They required more bedside surgery: 3 (11.5%) versus 11 (50.0%) ( $p=0.046$ ); and they required more primary drainage: 1 (5.6%) versus 10 (45.5%) ( $p=0.011$ ). Time to continuity restoration was longer: 52 days versus 72.5 days ( $p=0.038$ ); they were also older at discharge: 43.9 wGA versus 47.0 wGA ( $p=0.005$ ). Comparing surgical indications, neonates with failed medical treatment presented more persistent ductus arteriosus than those with pneumoperitoneum (7 (35.0%), versus 1 (4.8%);  $p=0.020$ ). They were operated later (53.3 hours, versus 16.5 hours;  $p=0.042$ ).

#### IV. Discussion

In this tertiary neonatal center cohort of 41 neonates surgically treated for NEC, 65.8% had adverse outcomes, defined as death or parenteral feeding requirement at term. On univariate analysis, adverse outcome was associated with surgical indication for hemodynamic shock (n=12 (52.2%); p=0.003), surgical revision (n=18 (66.7%); p=0.026) and proximal ostomy (n=17 (77.3%); p<0.001).

Gestational age and birth weight were not associated with death or parenteral feeding at term, like in studies looking at short-term outcome<sup>35,36</sup>. However, in the longer term, gestational age and being small for gestational age are predictive factors for death at 1 year's follow up<sup>19</sup>. Gestational age and birth weight do not impact short-term surgical outcome, but do impact long-term outcome.

Mortality was 22% at term, comparable to other studies reporting 37% mortality within 48 hours after surgery<sup>35</sup> and 23% at 28 days<sup>18</sup>. The present rate of parenteral feeding at term was 43.9%, which is similar to the study by Bethell al.<sup>18</sup> with 41% of patients requiring parenteral feeding 28 days after surgery, for a median 36 days. In a UK cohort<sup>19</sup>, 70% of patients required parenteral feeding at 28 days after the decision to intervene surgically, and this was associated with risk of death at 1 year's follow-up. The present high rate of adverse outcomes was similar to that in the literature, and underlines that NEC is a serious pathology.

Concerning surgical indications, patients who underwent surgery because of failed medical treatment due to persistent hemodynamic instability had more adverse outcomes than those operated on for pneumoperitoneum. Inotrope requirement itself was not associated with death or parenteral feeding at term. This may be explained by the high rate

of inotrope support in the present study: 57.1% of patients surviving without parenteral feeding at term required inotrope support at the time of surgery. In other studies<sup>18,19</sup>, the rate of inotrope support was lower, at 18-30%, and was associated with adverse outcomes. It seems that intensive care, such as inotrope support, is associated with adverse outcome.

Surgical revision before continuity restoration was associated with adverse outcome; it concerned 53% of patients, which was comparable to the literature<sup>32,33</sup>. Patients requiring surgical revision were more immature and possibly too sick to undergo complete primary surgery (**Table 4**). Severity seemed to be quickly identified, as 61.1% were operated on within 24 hours. They probably had rapidly worsening NEC with extensive necrotic bowel, as they were severely affected and there was no difference in surgical indications between infants with and without surgical revision. This factor could not be individualized in subgroup analysis. In the literature, data on surgical revision in NEC and outcomes are lacking.

Concerning surgical practices, 64.1% of neonates required an ostomy after the first surgery and 87.8% after surgical revision, which is comparable to the literature. Laparotomy with resection of necrotic bowel associated to ostomy is a common procedure<sup>35</sup>, because fecal contamination and systemic inflammation can preclude anastomosis. Ostomy level was strongly associated with adverse outcome, with a 77.3% rate of proximal ostomy in group death or parenteral feeding at term versus 14.3% in group free of parenteral feeding ( $p < 0.001$ ) and the difference was also significant in terms of death only ( $p < 0.045$ ). Proximal jejunal ostomy was associated with adverse outcome ( $p = 0.013$ ) and, conversely, distal ileum ostomy seemed to be associated with survival free of parenteral feeding ( $p = 0.002$ ). Although proximal ostomy is expected to be more strongly associated with adverse outcome, reflecting



the extent of necrosis and possibly leading to intestinal insufficiency<sup>37</sup>, those results shed light on the impact of distal ostomy. This also helps the clinician to define appropriate parenteral feeding goals depending on ostomy level. An observational study of enteral autonomy in neonates with ostomy showed that none of the infants with jejunostomy were able to achieve enteral autonomy, in contrast to colostomy, where infants did achieve enteral autonomy<sup>28</sup>. Considering stoma- and parenteral-related complications, time to reanastomosis is an important factor, with timing around 42 or 43 wGA in the above study. In our cohort, 21% of neonates were able to undergo reanastomosis before 41 wGA.

In our cohort, the principal indications leading to surgery, failed medical treatment and pneumoperitoneum, did not correlate with outcome, presumably due to lack of power and probably because we were unable to identify rapidly extending necrotic bowel NEC. This might explain why there were no differences in surgical indications between groups or on subgroup analysis. The decision-making process for surgery has been little studied in the literature, but is based mainly on clinical assessment<sup>18</sup>, except in case of pneumoperitoneum, which is a well-defined indication. Failed medical treatment and suspected necrotic bowel, compared to pneumoperitoneum, are associated with death or continuing parenteral feeding at 28 days<sup>18</sup>, and time to surgery according to indication was significantly different, being shorter with pneumoperitoneum. Favorable outcome according to surgery timing was also in favor of pneumoperitoneum ( $p=0.042$ ). Shorter time to surgery may improve outcome either because of the difference in indications leading to surgery, reflecting different underlying pathogenesis, or because of shorter exposure to inflammation.

In the literature, variations are wide, but the principal values are similar in our cohort, especially for the timing of and indication for surgery and for surgical practices. However, infants in this cohort were older in gestational age. Times to surgical revision were much longer than in the literature, where some other studies excluded revision after 7 days.

The main limitation of the present study was its retrospective observational design. The sample size may have led to a lack of power, limiting multivariate analysis. Parenteral feeding was assessed at term, and not at 28 days as in some other studies<sup>18,19</sup>, to overcome the bias due to prematurity. However, neonates were unexpectedly older in gestational age than in the literature, which could lead to overestimation of the number of patients needing parenteral feeding after surgery, as surgery could be close to term. Surgical indications could not be specifically predefined, but this allowed contemporary surgical practice to be studied, rather than practices influenced by strict definition. Identifying NEC with rapidly extending necrotic bowel could have helped refine the analyses. The strength of the study was to provide an overview of surgical management of NEC in a tertiary neonatal center, excluding spontaneous intestinal perforation, and with diagnosis proven on surgical records or histopathology.

This study confirmed that necrotizing enterocolitis is a disease with high risk of mortality and morbidity, and identified some risks factors. Infants undergoing surgery because of hemodynamic shock and needing surgical revision were at high risk of death or dependence on parenteral feeding. Most patients with proximal ostomy do not achieve enteral autonomy until reanastomosis, and are at risk of comorbidities. These points could help clinicians and

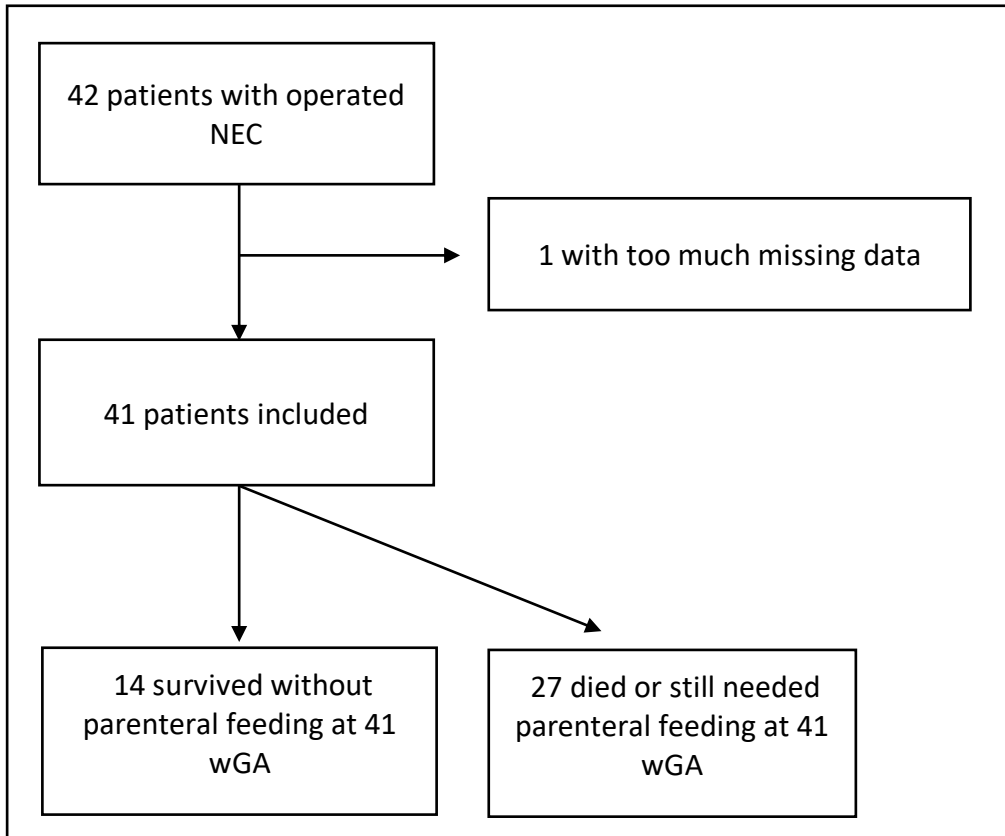
surgeons to discuss management and prognosis in NEC and to set suitable nutritional goals. They could also provide some elements for parent counseling.

## **V. Conclusion**

In this cohort of surgically managed NEC, performed in a tertiary NICU, two-third of the population presented the adverse outcome death, or parenteral nutrition requirement at term. These infants presented significantly more proximal ostomy and surgical revision. Principal surgery management was resection of necrotic bowel with ostomy. The review of the literature associated to our study showed a huge variation of practices. Larger prospective research may benefit to precise surgery indication and timing.

## VI. Figure and tables

Figure 1: Flowchart



**Table 1:** Neonatal characteristics.

	Parenteral-free survival N=14		Death or parenteral feeding N= 27		P-value
	n/median	%/IQR	n/median	%/IQR	
C-section, n=39	11	78.6	16	64.0	0.477
AC, n=40	7	53.8	18	66.7	0.498
Age at birth (wGA), n=41	30.2	29.8-33.3	29.1	27.4-33.4	0.433
Birthweight (grams), n=41	1,520	1,203-1,728	1,175	800-1,860	0.277
SGA, n=41	3	21.4	6	22.2	1.00
Female, n=41	6	42.9	14	51.9	0.744
PDA, n=41	0	0	8	29.6	<b>0.035</b>
BPD, n=39	2	14.3	9	36.0	0.266
CC-related infection, n=41	4	28.6	11	40.7	0.512
Treated PTR, n=38	0	0	1	4.2	1.00
IVH $\geq$ grade 3-4, n=41	1	7.1	0	0	0.341

*AC: antenatal corticosteroids. BPD: bronchopulmonary dysplasia. CC: central catheter. IVH: intraventricular hemorrhage. PDA: persistent ductus arteriosus. SGA: small for gestational age. PTR: preterm retinopathy. wGA: weeks gestational age.*

**Table 2:** Characteristics at time of necrotizing enterocolitis (NEC) diagnosis.

	Parenteral-free survival N=14		Death or parenteral feeding N= 27		P- value
	n/median	%/IQR	n/median	%/IQR	
Age at diagnosis (days), n=41	14	11.3 - 16.8	16	10.5 - 19	0.934
Age at diagnosis (wGA), n=41	33.8	31.4 - 35.0	32.0	30.1 - 34.9	0.371
<b>Bell Score, n=41</b>					
IIA, n=1	0	0	1	3.7	1.00
IIB, n=2	0	0	2	7.4	0.539
IIIA, n=16	4	28.6	12	44.4	0.501
IIIB, n=22	10	71.4	12	44.4	0.186
Pneumatosis <sup>a</sup> , n=41	10	71.4	15	55.6	0.501
Aeroportia <sup>a</sup> , n=41	2	14.3	8	29.6	0.447
Pneumoperitoneum <sup>a</sup> , n=41	10	71.4	11	40.7	0.100
Intubation due to NEC <sup>b</sup> , n=41	9	64.3	20	74.1	0.719
Bacterial infection <sup>c</sup> , n=41	6	42.9	16	59.3	0.346
Inotrope support, n=41	8	57.1	18	66.7	0.734

<sup>a</sup>Pneumatosis, aeroportia or pneumoperitoneum seen on X-ray before surgery. <sup>b</sup>Intubation due to respiratory instability; intubation for surgery was excluded. <sup>c</sup>Bacterial infection documented by hemoculture or peritoneal fluid. wGA: weeks gestational age.

**Table 3:** Characteristics of NEC surgical management.

	Parenteral-free survival N=14		Death or parenteral feeding N= 27		P-value	Percentage/ median in our population	Percentage / median in literature
	n/median	%/IQR	n/median	%/IQR			
Age at surgery (days), n=41	16	13.3 - 23.8	17	12.0 - 23.5	0.978	16.0	6-25
Corrected age at surgery (wGA), n=41	34.3	31.9 - 35.3	34.6	30.9 – 35.3	0.762	34.4	29-32
Weight at surgery (grams), n=41	1,875	1,384 – 2,194	1,530	1,303 – 1,885	0.329	1640	1687
Surgery timing (hours), n=36	48.0	22.0 – 89.0	24.0	5.50 – 59.5	0.323	34.9	37.2
Surgery timing <24h, n=36	4	30.8	12	52.2	0.301	44.4 %	*
Surgery on nightshift or holiday, n=39	7	58.3	19	70.4	0.486	66.7 %	*
Transfer from other NICU, n=41	10	71.4	11	40.7	0.100	51.2 %	74 %
<b>First surgery indication, n=41</b>							
Pneumoperitoneum, n=21	10	71.4	11	40.7	reference	51.2 %	50-55 %
Failed medical treatment, n=20	4	28.6	16	59.3	0.100	48.8 %	35-50 %
Occlusive syndrome	1	7.1	2	7.4	1.00	7.3 %	*
Hemodynamic shock	0	0.0	12	52.2	<b>0.003</b>	29.3 %	*
Respiratory instability	3	21.4	6	22.2	1.00	22.0 %	*
Other	2	14.3	6	22.2	0.692	19.5 %	*
<b>Characteristics of 1st Surgery</b>							
Surgery at bedside, n= 40	3	23.1	11	40.7	0.316	35.0 %	*
Primary drainage, n= 40	3	21.4	8	30.8	0.715	27.5 %	5-70 %
Ostomy, n=40	11	78.6	15	57.7	0.187	65.0 %	21-81 %
Incomplete laparotomy closure, n=40	1	7.1	5	19.2	0.399	15.0 %	*

NICU: neonatal intensive care unit. wGA: weeks gestational age. References: GS Bethell and M Knight, May 2021, AL Smazal and LA Massieu May 2020, JK Baelum and L Rasmussen April 2019, C Imren and LE Vlug July 2021, C Zozaya and IG Gonzalez May 2020, BDP Ta and E Roze December 2010, PM Garg and MM Hitt July 2020, BD Carr and SK Gadepalli March 2019, J Al-Hudhaif and S Phillips May 2009, A Svenningsson and H Borg May 2023, S Federici and L De Biagi Jun 2017, SM Han and CR Hong March 2020, TR Weber and JE Lewis April 1986. \*no data found.

**Table 3b:** Characteristics of NEC surgical management continued.

	Parenteral-free survival N=14		Death or parenteral feeding N= 27		P-value	Percent/ median in our population	Percent/ median in literature
	n/median	%/IQR	n/median	%/IQR			
<b>Surgical revision</b>							
Surgical revision, n=41	4	28.6	18	66.7	<b>0.026</b>	53.7 %	43-52 %
Time (hours), n=22	168	156 – 168	132	30 – 168	0.414	144	24-38
<b>Anatomic consequences</b>							
Length of SB resected (cm), n=27	6.00	0 – 20.0	21.5	3.00 – 25.8	0.390	19.0	15-29.2
Proximal ostomy, n=36	2	14.3	17	77.3	<b>&lt;0.001</b>	53.0 %	44.2 %
Conservation of ICV, n=36	8	61.5	10	43.5	0.489	50.0 %	21 %
Continuity restoration before 41 wGA, n=31	5	35.7	4	23.5	0.693	29.0 %	*
Time to continuity restoration (days), n=31	66.0	42.8 – 96.3	69.0	56.0 – 90.0	0.500	69.0	73-124

*ICV: ileocecal valve. NICU: neonatal intensive care unit. SB: small bowel. wGA: weeks gestational age. References: GS Bethell and M Knight, May 2021, AL Smazal and LA Massieu May 2020, JK Baelum and L Rasmussen April 2019, C Imren and LE Vlug July 2021, C Zozaya and IG Gonzalez May 2020, BDP Ta and E Roze December 2010, PM Garg and MM Hitt July 2020, BD Carr and SK Gadepalli March 2019, J Al-Hudhaif and S Phillips May 2009, A Svenningsson and H Borg May 2023, S Federici and L De Biagi Jun 2017, SM Han and CR Hong March 2020, TR Weber and JE Lewis April 1986. \*no data found.*



**Table 4:** Subgroup analysis: characteristics of infants according to surgical revision

	No surgical revision N=19		Surgical revision N=22		P-value
	n /median	% /IQR	n/median	% /IQR	
Age at birth (wGA), n=41	32.4	29.9-34.5	28.6	27.1-31.6	<b><u>0.004</u></b>
Weight at birth (g), n=41	1,720	1,295-2,023	1,025	823-1,380	<b><u>0.006</u></b>
PDA, n=41	2	10.5	6	27.3	0.249
Surgery indication: FMT, n=41	9	47.4	11	50.0	1.00
1 <sup>st</sup> surgery timing < 24h, n=36	5	27.8	11	61.1	0.092
Bedside surgery, n=40	3	16.7	11	50.0	<b><u>0.046</u></b>
Drainage, n=40	1	5.6	10	45.5	<b><u>0.011</u></b>
Primary ostomy, n=40	16	76.2	10	52.6	0.186
Time to continuity restoration (days), n=31	52.0	43.5-81.0	72.5	57.0-119	<b><u>0.038</u></b>
Age at discharge (days), n=32	85.5	75.0-105	117	103-184	<b><u>0.001</u></b>
Age at discharge wGA, n=32	43.9	43.2-46.0	47.9	45.2-54.3	<b><u>0.005</u></b>

*g: grams. PDA: Patent ductus arteriosus. FMT: Failed medical treatment. wGA: weeks gestational age.*

## VII. Supplemental tables

**Table 5:** Subgroup analysis: characteristics of infants according to surgical indication.

	Pneumoperitoneum N=21		Failed medical treatment N=20		P-value
	n /median	% /IQR	n/median	% /IQR	
Age at birth (wGA), n=41	32.0	29.7-33.7	28.5	27.4-32.3	0.144
Weight at birth (g), n=41	1,500	1,175-1,730	1,090	815-1,918	0.291
PDA, n=41	1	4.8	7	35	<b>0.020</b>
Vasoactive drugs, n=41	10	47.6	16	80.0	0.052
Intubation, n=41	10	47.6	19	95.0	<b>&lt;0.001</b>
Surgery timing (hours), n=36	16.5	4.50-48.0	53.3	26.8-128	<b>0.042</b>
Bedside surgery, n=40	5	23.8	9	47.4	0.186
Primary drainage, n=40	5	23.8	6	31.6	0.727
Primary ostomy, n=40	16	76.2	10	52.6	0.186
Surgical revision, n=41	11	52.4	11	55.0	1.000
Time to continuity restoration (days), n=31	69.0	54.0 – 94.5	59.5	44.3 – 89.8	0.417
Age at discharge (days), n=32	96.0	79.5 – 109	133	103 – 176	<b>0.027</b>

*g: grams. PDA: patent ductus arteriosus. wGA: weeks gestational age.*

**Table 6:** Surgical characteristics associated with death.

	Survival at term N=32		Death before term N=9		P-value
	n /median	% /IQR	n/median	% /IQR	
Surgery timing (hours), n=37	48	16.5-89.0	12.0	3.00-20.3	<b>0.034</b>
1 <sup>st</sup> surgery timing < 24h, n=37	11	37.9	5	71.4	0.294
Transfer from peripheral hospital, n=41	17	53.1	4	44.4	0.719
Surgery on nightshift or holiday, n=41	19	63.3	7	77.8	0.689
<b>First surgery Indication n=41</b>					
Pneumoperitoneum, n=21	19	59.4	2	22.2	Reference
Failed medical treatment, n=20	13	40.6	7	77.8	0.067
Occlusive syndrome	3	9.4	0	0.0	1.00
Hemodynamic shock	5	15.6	7	77.8	<b>&lt;0.001</b>
Respiratory instability	6	18.8	3	33.3	0.384
Other	6	18.8	2	22.2	1.00
<b>Characteristics of 1st Surgery</b>					
Surgery at bedside, n= 40	8	25.8	6	66.7	<b>0.044</b>
Primary drainage, n= 40	8	25.0	3	37.5	0.660
Primary ostomy, n=40	23	71.9	3	37.5	0.102
Incomplete laparotomy closure, n=40	5	15.6	1	12.5	1.00
Surgical revision, n=41	16	50.0	6	66.7	0.466
Proximal ostomy, n=36	14	45.2	5	100	<b>0.047</b>

**Table 7:** Ostomy level and outcome.

	Parenteral-free survival N=14		Death or parenteral feeding N= 27		P-value
	n	%	n	%	
<b>Ostomy level, n=36</b>					
Proximal jejunum	0	0	8	34.6	<b><u>0.013</u></b>
Distal jejunum	0	0	3	13.6	0.267
Proximal ileum	2	14.3	6	27.3	0.441
Distal ileum	11	78.6	5	22.7	<b><u>0.002</u></b>
Colic	1	7.1	0	0	0.389

THÈSE SOUTENUE PAR : Anouck GRANON

TITRE :

Association between surgical factors and severe outcome in infants with surgical necrotizing enterocolitis. A retrospective study from a tertiary neonatal intensive care unit

CONCLUSION :

In this cohort of surgically managed NEC, performed in a tertiary NICU, two-third of the population presented the adverse outcome, death or parenteral nutrition requirement at term. These infants presented significantly more proximal ostomy and surgical revision. Principal surgery management was resection of necrotic bowel with ostomy. The review of the literature associated to our study showed a huge variation of practices. Larger prospective research may benefit to precise surgery indication and timing.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 20/09/23

LE DOYEN DE LA FACULTÉ DE MÉDECINE

LE PRÉSIDENT / LA PRÉSIDENTE DU JURY

Pr Olivier PALOMBI

Pr Olivier PALOMBI  
Doyen de l'UFR de Médecine  
Par délégation  
du Président de l'UGA

Pr Thierry DEBILLON

## VIII. References

1. Han SM, Hong CR, Knell J, et al. Trends in incidence and outcomes of necrotizing enterocolitis over the last 12 years: A multicenter cohort analysis. *J Pediatr Surg.* 2020;55(6):998-1001. doi:10.1016/j.jpedsurg.2020.02.046
2. Zozaya C, García González I, Avila-Alvarez A, et al. Incidence, Treatment, and Outcome Trends of Necrotizing Enterocolitis in Preterm Infants: A Multicenter Cohort Study. *Front Pediatr.* 2020;8:188. doi:10.3389/fped.2020.00188
3. Abdullah F, Zhang Y, Camp M, et al. Necrotizing enterocolitis in 20,822 infants: analysis of medical and surgical treatments. *Clin Pediatr (Phila).* 2010;49(2):166-171. doi:10.1177/0009922809349161
4. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med.* 2011;364(3):255-264. doi:10.1056/NEJMra1005408
5. Meister AL, Doheny KK, Travagli RA. Necrotizing enterocolitis: It's not all in the gut. *Exp Biol Med Maywood NJ.* 2020;245(2):85-95. doi:10.1177/1535370219891971
6. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg.* 1978;187(1):1. doi:10.1097/00000658-197801000-00001
7. Frost BL, Modi BP, Jaksic T, Caplan MS. New Medical and Surgical Insights Into Neonatal Necrotizing Enterocolitis: A Review. *JAMA Pediatr.* 2017;171(1):83-88. doi:10.1001/jamapediatrics.2016.2708
8. Thompson AM, Bizzarro MJ. Necrotizing Enterocolitis in Newborns. *Drugs.* 2008;68(9):1227-1238. doi:10.2165/00003495-200868090-00004
9. Rees C, Hall N, Eaton S, Pierro A. Surgical strategies for necrotising enterocolitis: a survey of practice in the United Kingdom. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(2):F152-F155.

doi:10.1136/adc.2004.051862

10. Robinson JR, Rellinger EJ, Hatch LD, et al. Surgical necrotizing enterocolitis. *Semin Perinatol.* 2017;41(1):70-79. doi:10.1053/j.semperi.2016.09.020
11. Blakely ML, Lally KP, McDonald S, et al. Postoperative outcomes of extremely low birth-weight infants with necrotizing enterocolitis or isolated intestinal perforation: a prospective cohort study by the NICHD Neonatal Research Network. *Ann Surg.* 2005;241(6):984-989; discussion 989-994. doi:10.1097/01.sla.0000164181.67862.7f
12. Blakely ML, Tyson JE, Lally KP, et al. Laparotomy Versus Peritoneal Drainage for Necrotizing Enterocolitis or Isolated Intestinal Perforation in Extremely Low Birth Weight Infants: Outcomes Through 18 Months Adjusted Age. *Pediatrics.* 2006;117(4):e680-e687. doi:10.1542/peds.2005-1273
13. Moss RL, Dimmitt RA, Barnhart DC, et al. Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation. *N Engl J Med.* 2006;354(21):2225-2234. doi:10.1056/NEJMoa054605
14. Carr BD, Gadepalli SK. Does Surgical Management Alter Outcome in Necrotizing Enterocolitis? *Clin Perinatol.* 2019;46(1):89-100. doi:10.1016/j.clp.2018.09.008
15. Garg PM, Hitt MM, Blackshear C, Maheshwari A. Clinical determinants of postoperative outcomes in surgical necrotizing enterocolitis. *J Perinatol Off J Calif Perinat Assoc.* 2020;40(11):1671-1678. doi:10.1038/s41372-020-0728-8
16. Bell M, Cole CR, Hansen NI, et al. Neurodevelopmental and Growth Outcomes of Extremely Preterm Infants with Short Bowel Syndrome. *J Pediatr.* 2021;230:76-83.e5. doi:10.1016/j.jpeds.2020.11.026
17. Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal

perforation in preterm low birth weight infants. *Cochrane Database Syst Rev.* 2011;(6):CD006182. doi:10.1002/14651858.CD006182.pub2

18. Bethell GS, Knight M, Hall NJ, BAPS-CASS NEC Investigator Group on behalf of BAPS-CASS. Surgical necrotizing enterocolitis: Association between surgical indication, timing, and outcomes. *J Pediatr Surg.* 2021;56(10):1785-1790. doi:10.1016/j.jpedsurg.2021.04.028

19. Allin BSR, Long AM, Gupta A, Lakhoo K, Knight M. One-year outcomes following surgery for necrotising enterocolitis: a UK-wide cohort study. *Arch Dis Child Fetal Neonatal Ed.* 2018;103(5):F461-F466. doi:10.1136/archdischild-2017-313113

20. Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723-1729. doi:10.1164/ajrccm.163.7.2011060

21. Starr R, De Jesus O, Shah SD, Borger J. Periventricular And Intraventricular Hemorrhage. In: *StatPearls.* StatPearls Publishing; 2022. Accessed November 7, 2022. <http://www.ncbi.nlm.nih.gov/books/NBK538310/>

22. Occlusion intestinale aiguë | SNFGE.org - Société savante médicale française d'hépatogastroentérologie et d'oncologie digestive. Accessed November 7, 2022. <https://www.snfge.org/content/occlusion-intestinale-aigue-0>

23. Vargas MG, Miguel-Sardaneta ML, Rosas-Téllez M, Pereira-Reyes D, Justo-Janeiro JM. Neonatal Intestinal Obstruction Syndrome. *Pediatr Ann.* 2018;47(5). doi:10.3928/19382359-20180425-02

24. Schwarz CE, Dempsey EM. Management of Neonatal Hypotension and Shock. *Semin Fetal Neonatal Med.* 2020;25(5). doi:10.1016/j.siny.2020.101121

25. Di Muzio M, Dionisi S, Di Simone E, et al. Can nurses' shift work jeopardize the patient safety? A systematic review. *Eur Rev Med Pharmacol Sci.* 2019;23(10):4507-4519. doi:10.26355/eurrev\_201905\_17963



26. Amirian I. The impact of sleep deprivation on surgeons' performance during night shifts. *Dan Med J.* 2014;61(9):B4912.
27. Puckett Y, Caballero B, Dissanaike S, Richmond R, Ronaghan CA. Surgeons Maintain Better Focus Working 12-Hour Shifts Compared to 24-Hour Calls. *J Surg Educ.* 2021;78(4):1280-1285. doi:10.1016/j.jsurg.2020.12.008
28. Smazal AL, Massieu LA, Gollins L, Hagan JL, Hair AB, Premkumar MH. Small Proportion of Low-Birth-Weight Infants With Ostomy and Intestinal Failure Due to Short-Bowel Syndrome Achieve Enteral Autonomy Prior to Reanastomosis. *JPEN J Parenter Enteral Nutr.* 2021;45(2):331-338. doi:10.1002/jpen.1847
29. Imren CV Lotte E; de Koning, Barbara AE; Diertens, Tessa; Snel, Heleen E; Suurland, Jill; Swarte, Renate MC; Vermeulen, Marijn J; Keyzer Dekker, Claudia MG. Necrotizing Enterocolitis in a Dutch Cohort of Very Preterm Infants: Prevalence, Mortality, and Long-Term Outcomes. *Eur J Pediatr Surg.* 2022;32(01):111-119. doi:10.1055/s-0041-1741544
30. Ta BDP, Roze E, van Braeckel KNJA, Bos AF, Rassouli-Kirchmeier R, Hulscher JBF. Long-term neurodevelopmental impairment in neonates surgically treated for necrotizing enterocolitis: enterostomy associated with a worse outcome. *Eur J Pediatr Surg Off J Austrian Assoc Pediatr Surg Al Z Kinderchir.* 2011;21(1):58-64. doi:10.1055/s-0030-1267976
31. Federici S, DE Biagi L, Straziuso S, et al. Multicenter retrospective study on management and outcome of newborns affected by surgical necrotizing enterocolitis. *Minerva Chir.* 2017;72(3):183-187. doi:10.23736/S0026-4733.17.07159-0
32. Bælum JK, Rasmussen L, Qvist N, Ellebæk MB. Enterostomy complications in necrotizing enterocolitis (NEC) surgery, a retrospective chart review at Odense University Hospital. *BMC Pediatr.* 2019;19(1):110. doi:10.1186/s12887-019-1488-5

33. Weber TR, Lewis JE. The role of second-look laparotomy in necrotizing enterocolitis. *J Pediatr Surg*. 1986;21(4):323-325. doi:10.1016/s0022-3468(86)80194-4
34. Al-Hudhaif J, Phillips S, Gholum S, Puligandla PP, Flageole H. The timing of enterostomy reversal after necrotizing enterocolitis. *J Pediatr Surg*. 2009;44(5):924-927. doi:10.1016/j.jpedsurg.2009.01.028
35. Svenningsson A, Borg H, Hagander L, Engstrand Lilja H. Surgical management of necrotising enterocolitis in Sweden: A national cohort study. *Acta Paediatr Oslo Nor 1992*. 2023;112(8):1683-1688. doi:10.1111/apa.16836
36. Alexander F, Smith A. Mortality in micro-premature infants with necrotizing enterocolitis treated by primary laparotomy is independent of gestational age and birth weight. *Pediatr Surg Int*. 2008;24(4):415-419. doi:10.1007/s00383-008-2110-3
37. Sugarman ID, Kiely EM. Is there a role for high jejunostomy in the management of severe necrotising enterocolitis? *Pediatr Surg Int*. 2001;17(2-3):122-124. doi:10.1007/s003830000488

# Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ **Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

”