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## Safety and Efficacy of Ceftaroline in Neonates With Staphylococcal Late-onset Sepsis: A Case Series Analysis

Arnaud Callies, Lise Martin-Perceval, Lise Crémet, Lilas Gély, Anne Lise Ruellan, Marie-Clémence Verdier, Matthieu Grégoire, Cyril Flamant, Aurélie Guillouzouic, Sonia Prot-Labarthe, et al.

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4 Safety and Efficacy of Ceftaroline in Neonates With Staphylococcal Late Onset Sepsis: A Case  
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6 Series Analysis  
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**Abstract**

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3 Treatment of late-onset neonatal staphylococcal is sometimes challenging with feared side  
4 effects of vancomycin, increasing minimal inhibitory concentrations and questions about  
5 catheter management. In case of failure, ceftaroline was administered as a compassionate  
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8 treatment in 16 infants (gestational age of less than 32 weeks and less than 28 post-natal days),  
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11 whose first-line treatment failed. We report 11 successes and no severe adverse drug reactions.  
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15 Larger data are required to confirm these encouraging results.  
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## INTRODUCTION

Late-onset sepsis (LOS) with coagulase-negative staphylococci (CoNS) is often catheter-related, and associated with high morbidity in preterm neonates. The incidence is 4–11 per 1000 catheter days.<sup>1</sup> Vancomycin is the first-line treatment because of its narrow spectrum and activity against CoNS. Unfortunately, vancomycin heteroresistant CoNS strains have been increasingly reported worldwide.<sup>2</sup> Despite improvements through pharmacokinetic-model based adjustment, treatment with higher concentration of vancomycin could become necessary to guarantee a good efficiency (targeting AUC/MIC ratio > 400), which might increase oto- and nephrotoxicity. Also, some cases are affected by treatment failure. Daptomycin, linezolid or adjunction of rifampicin, are second-line therapies, all with notable adverse drug reactions (ADR).<sup>3</sup>

Ceftaroline, a 5<sup>th</sup> generation cephalosporin, is active against methicillin-resistant *Staphylococcus aureus* and CoNS and may be an alternative.<sup>4</sup> It has been approved by the European Medicines Agency in neonates from birth for complicated skin and soft tissue infections and community-acquired pneumonia. It has been used in exceptional circumstances, off-label, in preterm infants, and has demonstrated a good safety profile.<sup>5</sup>

In this study, we aimed to evaluate the efficacy and safety of ceftaroline for the treatment of neonatal LOS with staphylococci especially CoNS in infants born at < 32 weeks gestational age (GA) and < 28 post-natal days whose first-line treatment failed.

## MATERIAL AND METHODS

### Study design and patients

This single center retrospective case series study was conducted in a neonatal intensive care unit (NICU) in Nantes university hospital, France. Neonates born at < 32 weeks GA and <

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4 28 post-natal days presenting LOS with CoNS or *Staphylococcus aureus* from January 2018 to  
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6  
7 May 2022 were eligible if treated with ceftaroline after vancomycin failure. The decision to treat  
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9 was made at a multidisciplinary infectious diseases meeting. The reasons for rotation to  
10  
11 ceftaroline could be a persistent bacteremia), defined as positive blood cultures more than 48  
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13 hours apart despite effective vancomycin trough serum concentrations, acute kidney injury  
14  
15 (AKI), defined according to the Kidney Disease: Improving Global Outcomes' (KDIGO)  
16  
17 classification or clinical deterioration with bacteremia and ventilator-acquired pneumonia  
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19 (VAP).<sup>6</sup>  
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24 This study was observational and used anonymous data. In accordance with French  
25  
26 regulations, parents provided informed consent for medical data collection at admission.  
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#### 28 Study assessments

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31 Efficacy evaluation included assessment of clinical and microbiological responses at the  
32  
33 end of treatment (EOT) and 7 days later to identify potential recurrence of infection. Clinical  
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35 cure was defined as sepsis-related therapeutic de-escalation and resolution of physical symptoms  
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37 permitting discontinuation of antibacterial therapy. Clinical failure was defined as incomplete  
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39 resolution of physical symptoms or failure of sepsis-related therapeutic de-escalation.  
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43 Microbiological cure was defined as the eradication of the initial pathogen in blood cultures  
44  
45 without early or late recurrence. Microbiological failure was defined as the persistence of the  
46  
47 initial pathogen in blood cultures or its early or late recurrence, whether the bacteremia recurred  
48  
49 with the same pathogen before or after 72 h of EOT.  
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#### 52 Clinical analysis

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55 The following clinical data were collected from medical records and monitoring sheets:  
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57 sex, GA, postmenstrual age, birth weight, weight at the time of infection, coexisting medical  
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4 condition, vancomycin dose and duration, ceftaroline dose and duration, ceftaroline plasma  
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6 concentration when available, and catheter management (removal). Available biological  
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8 parameters were reviewed to identify ADRs.  
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11 The sepsis-related therapeutic escalation refers to the specific management of sepsis. We  
12  
13 recorded respiratory support (high-frequency oscillatory or conventional ventilation),  
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15 introduction of insulin, fluid boluses, and use of vasopressors.  
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19 ADRs that occurred after the start of treatment were assessed until the end of  
20  
21 hospitalization. We considered ADRs based on those reported in the summary of product  
22  
23 characteristics (SPC) of ceftaroline and signals from the pharmacovigilance database Vigilyze®  
24  
25 (the World Health Organization global individual case safety report database), the Micromedex-  
26  
27 DRUGDEX® and the Martindale databases. Severity was assessed according to the general  
28  
29 guideline of the National Cancer Institute Common Terminology Criteria for Adverse Events  
30  
31 (V5) classification and the imputability according to the Naranjo algorithm.<sup>7</sup>  
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### 34 35 Biologic analysis

36  
37 Bacterial isolates from blood cultures were identified using a Vitek MS spectrometer.  
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39 Ceftaroline MICs were determined using the Etest MIC strips, while vancomycin MICs were  
40  
41 measured using VITEK 2 method (AST-P631 cards, BioMérieux SA, France) and, controlled by  
42  
43 broth microdilution method (UMIC, Biocentric, France) for MICs values  $\geq 2$  mg/L. MICs  
44  
45 interpretation was performed according to 2021 EUCAST guidelines.  
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49 A vancomycin serum steady-state trough concentration ( $C_{\min}$ ) was considered as effective  
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51 when it was ten-fold above the MIC (arbitrary cut-off used in the unit as target for vancomycin  
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53 dosage).  
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4 Ceftaroline plasma concentrations were measured six hours after the start of at least the  
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6 fifth injection by an HPLC-UV method validated according to EMA criteria.  
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9 The duration of bacteremia before the introduction of ceftaroline was defined as the time  
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11 from the first to the last positive blood culture. Time to sterile culture was the time from the first  
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13 day of ceftaroline administration to the first negative blood culture.  
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### 16 Statistical Methods

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19 Analyses are regarded descriptive: We used the number, median (min – max) and range  
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21 to describe the results. Statistical Package for the Social Science (SPSS, IBM, USA, 2019) was  
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23 used for the statistical analysis.  
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## 28 **RESULTS**

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31 Sixteen infants met the inclusion criteria for this study (Table 1). The median GA, weight  
32  
33 at birth, and chronological age at sepsis were 25 weeks + 1 day (24+0-26+6), 725 g (485-910),  
34  
35 and 8 days (1-25). Fifteen had bacteremia with CoNS, one with *Staphylococcus aureus*, lasting a  
36  
37 median of 5 days (1-11) before the introduction of ceftaroline. Eight patients (50%) had their  
38  
39 catheters changed before end of ceftaroline (two days before to three days after initiation, except  
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41 for patient 13 whose catheter was changed 8 days before). Overall, they received 8 mg/kg/8h (3-  
42  
43 8.5) of ceftaroline with a one-hour infusion, for 7.5 days (4-13) and overall, 8 days antibiotic  
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45 therapy (1-11) from the first negative blood culture. Thirteen patients out of 16 (81%) had  
46  
47 successful treatment at EOT and 11/16 (69%) seven days later, including the one child with  
48  
49 *Staphylococcus aureus*. Sterilization of blood was systematically performed in less than three  
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51 days when treatment was successful. Patient 5 died of refractory bronchopulmonary dysplasia  
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53 after palliative care at EOT. Patient 7 experienced bacteremia recurrence on the sixth day of  
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4 Our usual practice tends to treat the patient without changing the catheter, given the  
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6 difficulties of its management in this population. Therefore, only patient 13 had a catheter  
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8 change during the 1st line treatment. Even if 5 patients (31%) were treated successfully without  
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10 catheter removal, three out of five therapeutic failures (all with CoNS) could have been avoided  
11  
12 since subsequent catheter removal allowed patients to be treated appropriately. This observation  
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14 reinforces the need to change the catheter in cases of persistent bacteremia, in contrary to our  
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16 usual practice in the hope vancomycin will be sufficient.  
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21 One severe necrotizing enterocolitis was reported, and intestinal events were frequent.  
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23 Ceftaroline has a broad spectrum and its use may have consequences on the intestinal  
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25 microbiota. Although cephalosporins have been widely used with good safety results, we cannot  
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27 exclude that necrotizing enterocolitis cases observed in our cohort were in fact induced by  
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29 ceftaroline. Moreover, two patients experienced mild hypereosinophilia, a probable ADR,  
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31 reported in the SPC of ceftaroline as rare. The patient presenting with severe cholestasis, an  
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33 ADR not described before, also had prolonged parenteral nutrition which makes it only a  
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35 possible ADR.  
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41 In the literature, the target for the treatment of community-acquired *S. aureus* skin  
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43 infections is to maintain a concentration 35% of the time above MIC. In intensive care unit, some  
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45 authors recommend a target of free-C<sub>min</sub>/MIC ratio up to 6.<sup>8</sup> Three of our successfully treated  
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47 patients has C<sub>min</sub>/C<sub>MI</sub> below this target but maintained above 1, as suggested by some authors.  
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49 The few dosages did not allow us to conclude whether lower targets could be generalized.  
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51 Whether failure is secondary to under dosage is debatable in patient 7: we hypothesized that  
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53 ceftaroline trough concentration could not be maintained at a sufficient level for eradication at a  
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55 dose of 6 mg/kg/8h.  
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4 The limited data available suggested a dose of 6 to 8.5 mg/kg/8h.<sup>5,9</sup> We suggest a dose of  
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6 8-8.5 mg/kg/8h (with catheter removal if persistent bacteremia) in all patients except in the case  
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8 of AKI stage 3 where we would recommend 3-4 mg/kg/8h.<sup>10</sup> No clinical breakpoints and  
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10 epidemiological cut-off values have been established for CoNS by EUCAST, but according to  
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12 our data, these dosing regimens should successfully eradicate strains with MICs of  $\leq 1$ mg/L  
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14 (EUCAST breakpoint for ceftaroline resistance in *S. aureus*).  
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19 The duration of ceftaroline treatment varies greatly. The duration of antibiotic therapy  
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21 recommended in the department is 7 days from the first negative blood culture, overall 10 days  
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23 in case of pneumonia. In practice, the duration was defined according to the clinical context  
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25 (change of the catheter, evolution of the child, VAP) and physician's experience. The  
26  
27 bactericidal effect of ceftaroline and results suggest that a shorter duration is possible. Indeed,  
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29 patient 16 received only 1 days ceftaroline after catheter removal and first negative blood  
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31 culture. Further studies are warranted to confirm this. Also, we are eagerly awaiting the results of  
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33 studies on the value of procalcitonin in defining the duration of antibiotic therapy in preterm  
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35 infants.  
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## 43 CONCLUSION

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45 To our knowledge, this is the first study reporting treatment of LOS with *staphylococci* in  
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47 preterm infants < 32 GA and < 28 days PNA, with a good safety profile and efficacy. Although  
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49 the number of participants is limited and the effect on microbiota should be monitored, these data  
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51 provide encouraging results, and support the initiation of further studies. Moreover, because of  
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53 its broad-spectrum and reduced monitoring, its use could be extended to other indications.  
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Table

Patient #	Gender	GA or PMA (weeks) and weight (g) respectively a) at birth b) at sepsis	Specific condition	Staphylococcus species and V/CFT MICs (mg/L)	Sepsis intensity	PCT ng/mL	CRP mg/L	Medical reason for CFT	Duration (days)					CFT posology (per dose in mg/kg) interval (h) length (d)	CFT concentration (µg/ml)	Catheter removal** for treatment*	Outcome microbiological / clinical at a) EOT b) 7 days later	Adverse effects possibly related to treatment, grade (G) severity according to CTCAE general guidelines, imputability according to Naranjo
									V	Effective V*	Bacteremia before CFT	Time to sterile culture after CFT	ATB after first negative culture					
<u>1</u>	M	a)24+5 ; 715 b)25+6 ; 745	Diaphragmatic hernia	SC (1.0/0.25) SH (1.0/ 1.0)	HFO Dopa Insuline FB	NR	<5	AKI 1	4	4	2	NA	6	8.5 - 8 - 4	-	No	a) CC / E b) CC / E	
<u>2</u>	M	a)24+5 ; 750 b)25+6 ; 840	NEC 3	SC (1.0/0.38)	HFO Dopa Insulin	11.5	198	AKI 1 PB	4	5	4	NA	11	8.5 - 12 - 9	-	A	a) CC / E b) CF / LR	
<u>3</u>	F	a)25+4 ; 870 b)27+4 ; 970	NEC 2	SC (<0.5/0.38) SH (2.0/1.5)	-	NR	<5	PB	7	4	7	2	7	8.5 - 8 - 8	5.9	B	a) CC / E b) CC / E	
<u>4</u>	F	a)26+6 ; 575 b)28+5 ; 754		SC (<0.5/0.5) SW (1.0/0.38)	VACI Filling	2.84	<5	AKI 2 PB	10	11	10	NA	9	3.5 - 8 - 1 8 - 8 - 8	3.6	B	a) CC / E b) CC / E	Cholestasis, G1, possible
<u>5</u>	M	a)24 ; 600 b)24+5 ; 620	Umbilical inflammation <sup>1</sup>	SH (1.0/1.0)	Dopa VACI Insulin	NR	<5	AKI 1 PB	8	8	3	1	NA	6 - 8 - 7	-	No	a) CF / E b) NA	AKI 2, G2, possible
<u>6</u>	M	a)24+4 ; 670 b)25 ; 620	VAP NEC 3	SH (1.0/1.0)	Dopa HFO	0.84	28	VAP PB	14	14	8	NA	8	6 - 8 - 6	5.5	B	a) CC / E b) CC / E	
<u>7</u>	F	a)25 ; 785 b)25+4 ; 720		SH (1.0/1.0)	Dopa HFO Insulin	2.22	7.5	AKI 1 PB	9	9	8	1	NA	6 - 8 - 6 8 - 8 - 3	-	B	a) CF / P b) NA	
<u>8</u>	M	a)25+1 ; 780 b)26 ; 795		SE (1.0/0.12) SW(0.25/0.12)	Insulin	2.54	10.4	PB	4	4	5	1	7	6 - 8 - 8	4.5	A	a) CC / E b) CF / ER	Diarrhea, G1, possible
<u>9</u>	F	a)26+1 ; 791 b)27+4 ; 875		SE (1.0/0.38)	-	0.58	<5	PB	3	3	4	2	6	8 - 8 - 8	-	B	a) CC / E b) CC / E	
<u>10</u>	F	a)25+2 ; 485 b)28+1 ; 685	Severe IUGR VAP	SE (2.0/0.25) SH (<0.25/1.0)	HFO Insulin	0.82	14.8	VAP B	5	5	1/7 <sup>3</sup>	5/2 <sup>4</sup>	11	8 - 8 - 13	-	No	a) CC / E b) CC / E	Hypereosinophilia, G1, probable
<u>11</u>	M	a)24 ; 665 b)26+6 ; 695		SE (1.0/1.0) SH (2.0/1.0)	VACI Insuline	41	32	PB AKI 1	15	11	11	NA	10	8.5 - 8 - 7	-	B	a) CC / E b) CC / E	NEC (Bell 1), G2, possible
<u>12</u>	F	a)25+6 ; 678 b)26+2 ; 620	Neonatal kidney injury <sup>2</sup>	SH (1.0/1.0)	-	1.93	9.3	PB AKI 3	5	3	5	NA	NA	3 - 8 - 4	3.8	A	a) CF / P b) NA	
<u>13</u>	M	a)26+6 ; 900 b)27+3 ; 905	NEC grade Severe BPD	SH (0.5/1.0)	Dopa FB VACI Insulin	NR	23.5	VAP	8	4	1	NA	11	8 - 8 - 6	-	B	a) CC / E b) CC / E	AKI 1, G1, possible Cholestasis, G3, possible
<u>14</u>	F	a)25+6 ; 605 b)26+1 ; 620		SC (1.0/0.19) SE (2.0/0.25)		NR	<5	AKI2	12	10	5	NA	8	8 - 8 - 6	-	No	a) CC / E b) CC / E	AKI 2, G1, possible NEC (Bell 1), G2, possible
<u>15</u>	F	a)25+2 ; 910 b)28+5 ; 715	Severe BPD VAP	SA (0.5/0.38)	HFO	NR	<5	VAP	4	4	1/1 <sup>5</sup>	NA	8	8 - 8 - 6	-	No	a) CC / E b) CC / E	Diarrhea, G1, possible Hypereosinophilia,G1, possible
<u>16</u>	F	a)25+1 ; 735 b)28+5 ;1090	Candida bacteriema	SE (1.0/0.25)	VACI	1.07	<5	AKI1 PB	6	6	7	3	1	8 - 8 - 4	-	B	a) CC / E b) CC / E	NEC (Bell 2), G3, possible

**Table 1: Description of population and results**

ATB : Antibiotics; AKI: Acute Kidney Injury (stage); BPD: BronchoPulmonary Dysplasia; CC : clinical cure; CF : clinical failure; CFT: Ceftaroline; CRP: maximal protein-C reactive; CTCAE : Common Terminology Criteria for Adverse Events (V5) classification; E: Eradication; EOT: End Of Treatment; ER: Early Recurrence; F: Female; FB : fluid bolus; GA : gestational age; IUGR: Intra-Uterine Growth Retardation; LR: Late recurrence; M: Male; NA ; not applicable; NEC: Necrotizing enterocolitis (stage); P: Persistent; PB: Persistent Bacteriemia; PCT: maximal procalcitonin; PMA : post menstrual age; SA: *S. aureus*; SC: *S. capitis*; SE: *S. epidermidis*; SH: *S. haemolyticus*; SW: *S. warnerii* ;V: Vancomycin; VAP: Ventilation acquired pneumonia;

\*Patients with clinical failure of CFT treatment are underlined, \*sum of days with effective vancomycinemia; \*\*Catheter removal: A: after CFT treatment; B: before end of CFT

<sup>1</sup>Umbilical inflammation motivating vancomycin initiation 5 days before bacteremia occurred; <sup>2</sup>Kidney injury because of twin-to-twin transfusion syndrome; <sup>3</sup>1 day bacteremia and 7 days positive protected bronchial sampling; <sup>4</sup>5 days for sterile protected bronchial sampling and 2 days for sterile hemoculture; <sup>5</sup>1 day bacteremia and 1 day positive protected bronchial sampling