STRATEGIC TRIALS TO DEFINE THE BEST AVAILABLE TREATMENT FOR NEONATAL AND PAEDIATRIC SEPSIS CAUSED BY CARBAPENEM RESISTANT ORGANISMS

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ABSTRACT

The optimal standard of care for carbapenem-resistant bloodstream infections in children is currently unknown. This systematic review, aiming to define the best available treatments to be compared with new antibiotics in clinical trials, clearly points out the paucity of available data. The simplification and a wider harmonisation of study design are a global priority to inform the best strategies to treat these life-threatening infections in children.

BACKGROUND

Despite progress on child mortality rates, severe bacterial infections still cause significant morbidity and mortality in children and neonates [1]. Due to the extensive use of carbapenems during the last decades, carbapenem-resistant organisms (CROs) bloodstream infections (BSIs) have become a critical global health challenge, especially in low and middle-income countries [2-3]. These infections are either acquired from the mother around the time of delivery, from the community or in a healthcare facility.

Despite this increasing burden, the optimal treatment for CRO infections is still unknown due to the paucity of large randomized clinical trials (CTs) evaluating the effectiveness of various therapeutic approaches [4-5]. Recommendations are mostly derived from case reports, small case series and cohort studies with high heterogeneity in the treatment options evaluated. In one study, combination therapy with at least two agents showed a significant reduction in mortality compared to monotherapy [6]. Antibiotics currently available for CRO infections include aminoglycosides, polymyxins, tigecycline and fosfomycin. Since their marketing approval, most of these old drugs have not been subject to modern drug development procedures and information on their clinical use are scarce with several important concerns about limited efficacy, increased resistance and specific toxicities [7].

Despite the fact that there are new agents for CRO registered or in late stage clinical development, the lack of definition for the best available treatment to be used as standard of care (SOC) hampers the conduct of properly-designed paediatric/neonatal CTs. Therefore, the aim of this study was to systematically review the published evidence on the effectiveness of the antibiotic regimens commonly used for CRO sepsis in children in the attempt to establish the best available SOC and inform the design of future CTs.

METHODS

On the 5th of September 2017, MEDLINE (Ovid MEDLINE(R) without Revisions 1996 to August Week 4 2017) and EMBASE (Embase 1996 to 2017 Week 36) databases were systematically searched using a strategy combining MeSH and free-text terms for antibiotics *AND* Gram-negatives *AND* resistance to carbapenems in children (age range 0-18 years). The full search strategy is available in the Supplementary data.

Studies published in English, German, Italian, French, Polish, Greek, Dutch, Hungarian, Portuguese and Spanish were considered for inclusion.

Studies reporting data on 1) the single-patient level outcome related to 2) a specific antibiotic treatment 3) for BSIs 4) caused by carbapenem-resistant Gram-negatives 5) in children were included. Studies reporting data on other (non-BSIs) infections were excluded. Studies reporting data from both adults and children were included only if single-child level information could be identified.

RESULTS

The search identified 5,246 papers of which 16 fulfilled both inclusion and exclusion criteria and were included in the analysis (Supplementary Figure 1) [8-23]. Overall, outcome data was available for 61 patients, 67% (41/61) aged below than 3 months and 62% (38/61) of which were neonates. All the patients included were admitted to Intensive Care Unit, and all were reported to have comorbidities. According to the 2018 World Bank Classification [24], 7 studies were carried out in high-income [8-9, 12, 14, 17-18, 22] and 9 in middle-income countries [10-11, 13, 15-16, 19-21, 23].

Regarding the causative pathogens, 29 out of 62 isolates (one patient had 2 isolates) were *Klebsiella pneumoniae*, 22 *Acinetobacter baumannii*, 7 were *Escherichia coli* and 4 were *Enterobacter cloacae*. The genetic carbapenemase responsible for the resistance trait was available only for 38 isolates (Table 1).

27 out of 61 children (44%) received monotherapy whereas 34 (56%) were treated with a combination of two or more antibiotics. Overall, 27 different antibiotic regimens were reported, 8

including one and 19 including multiple drugs. The most frequently used regimen included carbapenems plus polymyxins (12 out of 27). Information on dosing was available only for 3 out of 61 patients.

Among the entire cohort, the case fatality rate was 36% (22/61), 12 of which were neonates (Box 1). The mortality was higher in patients receiving monotherapy (11/27, 41%) compared with children treated with antibiotic combinations (11/34, 32%).

DISCUSSION

This study clearly points out the paucity of data available on the treatment for children with CRO BSIs. Single-patient data were available for 61 children only, with a very wide variation in the prescribed regimens.

Although being the most comprehensive review available on the topic, this study has several limitations. Firstly, the limited number of included papers and the very small sample size did not permit any statistical analysis. Secondly, due to the lack of specific information provided by the authors, it was not possible to distinguish empiric versus targeted treatment in the evaluation of patients' outcome. For the same reason, we could not stratify patients based on the concordance or discordance of treatment, as the single pathogens' full resistance profiles were rarely reported. We found a huge heterogeneity in the included studies in terms of study design, population and pathogens of interest. Lastly, because of the small sample size, all the Gram-negative organisms have been grouped together.

Considering the worldwide increase in antimicrobial resistance, the high mortality rates, and the very limited options available for treating these infections in children, the need to conduct CTs selectively on CRO in this population is now crucial to identify the best available treatment. However, CRO infections are rare in children in Europe, making an adequate sample size difficult to achieve. Second, enrolling a patient into a clinical trial with limited therapeutic options can raise ethical issues if the infecting pathogen is resistant to one of the comparator agents [25].

Even if CTs on new antibiotics are now mostly relying on a non-inferiority strategy, the design of antibacterial trials expecting to demonstrate a non-inferiority over the comparator is broadly unrealistic in case of non-susceptible multidrug-resistant (MDR) pathogens [26]. To overcome this problem, it has been suggested to design specific antibiotics CTs only focused on MDR infections. However, these studies might be difficult to design, are costly, and difficult to complete. Furthermore, being selected as a suitable centre to recruit to CTs of MDR infections, because of the high rate of antimicrobial resistance, may be of concern to specific institutions.

However, it is not feasible for antibacterial drugs that treat serious resistant bacterial infections to be developed using traditional, large scale CTs due to the limited numbers of patients in which these serious infections occur. For this reason, the Limited Population Antibacterial Drug (LPAD) mechanism, a new pathway to speed up patient access to critically-needed antibiotics, has been recently proposed for adults [27]. This pathway aims to overcome the problem of widespread untargeted use of new antibiotics, at the same time reducing the barriers to drug development and approval process by framing MDR infections as “orphan diseases”. A drug’s safety and effectiveness could therefore be studied in smaller, more rapid, and less expensive CTs in small, well-defined populations of patients for whom the drug’s benefit has been shown to outweigh its risks [28].

Adult data on CRO treatment are also limited, and paediatric drug research is often based on small-scale studies that lack the statistical power necessary to draw any firm conclusion. However, the single dose PK single arm study approach that has been recently proposed is not sufficient here to inform the best available treatment [29]. In this case, CRO-focused strategic trials where the optimal drug combination can be studied using both off-patent and new antibiotics should be adopted. By using an all-comers approach, children of different ages with probable or proven CRO BSIs could be enrolled in a multi-dose study investigating the efficacy of different treatment regimens. This approach would also include neonates. If possible, adolescents should be included and enrolled in adult LPAD CTs, pooling controls across different age groups, and recruited globally.

The treatment of paediatric CRO infections is a challenge worldwide, and the paucity of published data don't allow, at the moment, to establish the best available therapeutic scheme. A joint effort between the various stakeholders is crucial to overcome the multiple barriers to conducting CTs and guarantee safe and effective therapies. Paediatric and neonatal CTs using simple and standardised trial designs are now a global priority in order to inform the optimal management of these life-threatening infections.

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Table 1: Characteristics of included studies

Study N	Author	Country	Study design	Age	Types of patients	CR* Pathogen	Carbapenemase	Treatment 1	Days of treatment	Treatment 2	Days of treatment	Treatment 3	Outcome
1	**Bonfanti P, 2016 [8]**	Italy	Case report	neonate	Mother-to-child transmitted at birth – NICU**	K. pneumoniae	KPC	Colistin	10	Meropenem	10	.	Survived
2	**Dara JS, 2013 [9]**	US	Retrospective	8 years	PICU***	K. pneumoniae	.	Polymyxin B	14	Rifampin	14	.	Survived
				3 years	Renal transplanted	K. pneumoniae	.	Polymyxin B	14	Rifampin	14	.	Survived
3	**Datta S, 2014 [10]**	India	Prospective study	neonate	Prematurity, NICU	E. coli	NDM-1	Piperacillin-tazobactam	.	Amikacin	.	.	Survived
				neonate	Prematurity, NICU	E.coli	NDM-1	Piperacillin-tazobactam	.	Amikacin	.	.	Survived
				neonate	NICU	K. pneumoniae	NDM-1	Colistin	.	.	.	.	Survived
				neonate	Prematurity, NICU	K. pneumoniae	NDM-1	Ofloxacin	.	.	.	.	Survived
				neonate	Prematurity, NICU	K. pneumoniae	NDM-1	Ofloxacin	.	.	.	.	Survived
				neonate	NICU	K. pneumoniae	NDM-1	Colistin	.	.	.	.	Survived
				neonate	Prematurity, NICU	E. coli	NDM-1	Meropenem	.	.	.	.	Dead

				neonate	Prematurity, NICU	K. pneumoniae	NDM-1	Meropenem	.	.	.	.	Survived
				neonate	Prematurity, NICU	E. cloacae, E. coli	NDM-1	Colistin	.	.	.	.	Survived
				neonate	NICU	E. coli	NDM-1	Ofloxacin	.	.	.	.	Survived
				neonate	Prematurity, NICU	E. cloacae	NDM-1	Piperacillin-tazobactam	.	Amikacin	.	.	Dead
				neonate	Prematurity, NICU	E. coli	NDM-1	Ofloxacin	.	.	.	.	Survived
4	**Escobar Perez JA, 2012 [11]**	Colombia	Outbreak report	neonate	Prematurity, NICU	K. pneumoniae	NDM-1	Meropenem	.	Rifampin	.	.	Survived
				neonate	NICU	K. pneumoniae	NDM-1	Imipenem	.	Ciprofloxacin	.	.	Survived
				neonate	Prematurity, NICU	K. pneumoniae	NDM-1	Imipenem	.	Ciprofloxacin	.	.	Dead
				neonate	NICU	K. pneumoniae	NDM-1	Imipenem	.	Ciprofloxacin	.	.	Survived
5	**Falagas ME, 2009 [12]**	Greece	Retrospective	14 months	PICU	A. baumannii	.	Colistimethate	10	Imipenem/ cilastatin	.	.	Improved
				11 years	PICU	K. pneumoniae	.	Colistimethate	10	Vancomycin	.	.	Improved
6	**Hurtado IC, 2012 [13]**	Colombia	Retrospective	3 years	Liver transplant	K. pneumoniae	KPC	Tygecicline	5	Gentamicin	.	.	Improved
				8 months	Premature, immunodeficiency	K. pneumoniae	KPC	Tygecicline	7	Amikacin	.	.	Dead

				4 months	Premature	K. pneumoniae	KPC	Tygecicline	17	Amikacin	.	.	Survived
7	**Lo A, 2010 [14]**	US	Case report	2 years	Ex premature, hydrocephalus	E. cloacae	KPC	Levofloxacin	.	Amikacin	.	.	Survived
8	**Malande OO, 2016 [15]**	South Africa	Retrospective	6 months	Cardiopathy, PICU	K. pneumoniae	GES	Colistin	14	.	.	.	Dead
				4 months	Liver transplant	K. pneumoniae	.	Colistin	14	Imipenem	14	.	Survived
				1 year	Liver transplant, PICU	K. pneumoniae	.	Colistin	4	.	.	.	Dead
				7 years	PICU	K. pneumoniae	NDM	Colistin	10	Imipenem	10	.	Survived
				3 years	PICU	K. pneumoniae	.	Colistin	14	Imipenem	14	.	Survived
				5 months	PICU	K. pneumoniae	.	Colistin	1	Meropenem	1	.	Dead
9	**de Oliveira MS, 2013 [16]**	Brazil	Retrospective	16 years	Acute abdomen, PICU	A. baumannii	.	Ampicillin/ sulbactam	16	.	.	.	Survived
				7 years	Burn, PICU	A. baumannii	.	Ampicillin/ sulbactam	9	.	.	.	Dead
				7 years	Heart failure, PICU	A. baumannii	.	Ampicillin/ sulbactam	3	.	.	.	Dead
10	**Oteo J, 2010 [17]**	Spain	Retrospective	3 months	PICU	E. cloacae	VIM-1	Amikacin	.	Cotrimoxazole	.	.	Survived
11	**Pannaraj PS, 2014 [18]**	US	Retrospective	7 months	BMT	K. pneumoniae	KPC-3	Ertapenem	.	Meropenem	.	Colistin	Dead

				3 years	PICU	K. pneumoniae	NDM-1	Imipenem	.	Colistin	.	.	Survived
				2 years	Myelodysplastic syndrome	E. coli	NDM-1	Imipenem	.	Amikacin	.	.	Dead
12	**Qamar MU, 2015 [19]**	Pakistan	Retrospective	neonate	NICU	K. pneumoniae	NDM-1	Ceftazidime	.	Imipenem	.	.	Dead
13	**Roy S, 2011 [20]**	India	Retrospective	neonate	NICU	K. pneumoniae	NDM-1	Colistin	.	Minocycline	.	.	Survived
14	**Thatrimontrichai A, 2013 [21]**	Thailand	Retrospective	neonate	NICU	A. baumannii	.	Ceftazidime	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Cefperazone/ sulbactam	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Cefperazone/ sulbactam	.	.	.	.	Survived
				neonate	NICU	A. baumannii	.	Cefperazone/ sulbactam	.	.	.	.	Survived
				neonate	NICU	A. baumannii	.	Vancomycin	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Imipenem	.	.	.	.	Survived
				neonate	NICU	A. baumannii	.	Imipenem	.	.	.	.	Survived
				neonate	NICU	A. baumannii	.	Imipenem	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Imipenem	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Imipenem	.	Cefoperazone/ sulbactam	.	.	Survived

				neonate	NICU	A. baumannii	.	Colistin	.	.	.	.	Dead
				neonate	NICU	A. baumannii	.	Colistin	.	.	.	.	Survived
				neonate	NICU	A. baumannii	.	Colistin	.	Cefoperazone/ sulbactam	.	.	Survived
15	**Tsiatsiou O, 2015 [21]**	Greece	Prospective study	neonate	SGA, NICU	A. baumannii	OXA-51-like and OXA-58	Meropenem	.	Colistin	.	.	Survived
				neonate	NICU	A. baumannii	OXA-51-like and OXA-58	Meorpenem	.	.	.	.	Survived
				6 weeks	Prematurity, NICU	A. baumannii	OXA-51-like and OXA-58	Meropenem	.	Colistin	.	.	Survived
				neonate	Prematurity, NEC, NICU	A. baumannii	OXA-51-like and OXA-58	Meropenem	.	Colistin	.	.	Survived
				11 weeks	Prematurity, renal failure, NICU	A. baumannii	OXA-51-like and OXA-58	Meropenem	.	Colistin	.	.	Dead
16	**Zhang XY, 2015 [22]**	China	Retrospective	neonate	NEC, NICU	K. pneumoniae	NDM-1	Meropenem	.	Ciprofloxacin	.	.	Dead
				neonate	Pneumonia, NICU	K. pneumoniae	NDM-1	Ceftazidime	.	.	.	.	Survived
				neonate	Pneumonia, NICU	K. pneumoniae	NDM-1	Piperacillin/ tazobactam	.	Ceftazidime	.	.	Poor prognosis

*CR: carbapenem-resistant; **NICU: Neonatal Intensive Care Unit; ***PICU: Paediatric Intensive Care Unit

Box 1: Neonatal data

	N	Dead patients
Total number	38	12
Pathogen		
K. pneumoniae	15	4
A. baumannii	16	6
E. coli	6	1
E. cloacae	2	1
Treatment regimen		
Monotherapy	22	7
Combination	16	5
Antibiotics		
Polymyxins	5	1
3rd gen- cephalosporins	5	2
Glycopeptides	1	1
Carbapenems	7	3
Fluoroquinolones	4	0
Carbapenems + Polymyxins	3	0
Carbapenems + Rifampin	1	0
Carbapenems + Fluoroquinolones	4	2
3rd gen- cephalosporins + Carbapenems	2	1
Polymyxins + Tetracyclines	1	0
3rd gen- cephalosporins + Polymyxins	1	0
Pip-tazobactam + Aminoglycosides	3	1
3rd gen- cephalosporins + Pip-tazobactam	1	1

Supplementary digital content

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SEARCH STRATEGY

MEDLINE (Ovid MEDLINE(R) without Revisions 1996 to August Week 4 2017) and EMBASE (Embase 1996 to 2017 Week 36). Searched on 05/09/2017

1. antibiotic.mp. or exp Anti-Bacterial Agents/
2. antimicrobial.mp.
3. (anti?biot* or anti?infect* or anti?bact* or anti?microb*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. anti microbial.mp.
5. exp Anti-Infective Agents/ or anti-infective.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Enterobacteriaceae/ or enterobacteriaceae.mp.
8. exp Enterobacter aerogenes/ or enterobacter.mp. or exp Enterobacter/ or exp Enterobacter cloacae/
9. exp Escherichia/ or escherichia.mp. or exp Escherichia coli/
10. klebsiella.mp. or exp Klebsiella/ or exp Klebsiella pneumoniae/ or exp Klebsiella oxytoca/
11. exp Morganella morganii/ or exp Morganella/ or morganella.mp.
12. proteus.mp. or exp Proteus/
13. serratia.mp. or exp Serratia/ or exp Serratia marcescens/
14. acinetobacter.mp. or exp Acinetobacter baumannii/ or exp Acinetobacter/
15. citrobacter.mp. or exp Citrobacter freundii/ or exp Citrobacter/ or exp Citrobacter rodentium/ or exp Citrobacter koseri/
16. exp Pseudomonas aeruginosa/ or exp Pseudomonas/ or pseudomonas.mp.
17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. extended spectrum beta-lactamases.mp.
19. ESBL.mp.

20. exp beta-Lactamases/ or carbapenemase.mp.
21. carbapenem resistance.mp.
22. carbapenem resistant.mp.
23. drug resistance.mp. or exp Drug Resistance/
24. carbapenemase*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25. (carbapenem adj1 resist*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26. CTX-M.mp.
27. AmpC.mp.
28. MBL.mp.
29. metallo-b-lactamase.mp.
30. vim.mp.
31. NDM.mp.
32. OXA.mp.
33. oxacillinase.mp.
34. IMP.mp.
35. KPC.mp.
36. Klebsiella pneumoniae carbapenemase.mp.
37. TEM.mp.
38. SHV.mp.
39. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 6 and 17 and 39
41. 40 not animals.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
42. limit 41 to "all child (0 to 18 years)"

Figure Supplementary 1: Flowchart and study selection