Treatments for complicated urinary tract infections (cUTI) caused by multidrug resistant (MDR) Gram-negative (GN) pathogens- a systematic review and network meta-analysis (NMA)

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Background

Worldwide, multidrug-resistant (MDR) pathogens are emerging, and it is predicted that this will lead to a shortage of potent antibiotics. This situation has become of high concern from leading health authorities. In 2017, the World Health Organization (WHO) highlighted the significant nature of antimicrobial resistance (AMR) and specified priority pathogens that new drugs are urgently needed to address. According to the WHO, pathogens considered "Priority 1 Critical" in this list are:

Acinetobacter baumannii, carbapenem resistant (CR),
Pseudomonas aeruginosa, CR
Enterobacteriaceae, CR, 3rd generation cephalosporin-resistant

Cefiderocol (CFDC) is a new siderophore-cephalosporin with a wide activity spectrum covering all aerobic GN pathogens including all WHO critical priority pathogens, that was recently approved by FDA for the treatment of GN cUTI in susceptible organisms.

Network meta-analysis (NMA) is a technique that can be used to obtain estimates of comparative effectiveness where treatments have not been compared directly in a head to head trial but can be linked by one or more common comparators based on the randomised controlled trials (RCTs) within which they have been compared. NMA is a method widely accepted method among health technology assessment (HTA) bodies and has been used extensively in HTA submissions in many countries.

A NMA is able to take into account and estimate the relative efficacy of multiple agents using any number of RCTs. Typically SLR is used as the evidence generation process for an NMA, ensuring that all relevant RCT evidence will be included in establishing relative effectiveness. However, NMAs present significant challenges when applied to antimicrobials relative effectiveness assessment, due to different pathogen coverage and mechanisms of resistance covered by each drug (figure 1) and included in RCTs, evolving resistance patterns of pathogens, geographical variations, heterogeneous population definition and measurements, range of severity of illness and non-inferiority trial designs. The use of established data synthesis methods, typically used to support HTA and decision makers, are challenged by these limitations and complexities associated with antimicrobials and disease area.

Figure 1: pathogen coverage spectrum by different treatment options

	Nonfermenters					Fermenters		
	P. aeruginosa			*A. baumannii*	*S. maltophilia*	Enterobacterales		
	Serine-carbapenemases*	Metallo-carbapenemases*	Other resistance mechanisms		Intrinsic carbapenem resistance*	β-lactamases (including ESBLs)	Serine-carbapenemase*	Metallo-carbapenemase*
Ceftolozane-tazobactam	●	●	●	●	●	●	●	●
ceftazidime-avibactam	●	●	●	●	●	●	●	●
Doripenem	●	●	●	●	●	●	●	●
Levofloxacin	●	●	●	●	●	●	●	●
Cefiderocol	●	●	●	●	●	●	●	●
Imipenem	●	●	●	●	●	●	●	●

Legend: ● Activity reported; ● Indeterminate clinical activity; ● No clinically relevant activity

Objectives

The objective of this analysis was to perform a systematic literature review (SLR) to identify RCT evidence and conduct indirect treatment comparison (ITC) with the data identified to understand the relative efficacy and safety of current treatment options for cUTI caused by MDR GN pathogens.

Methods

A systematic literature review (SLR) was conducted to identify all relevant trials that investigated the efficacy and safety of any parenterally administered antibiotic (or combination of antibiotics), at any dose, for the treatment of Gram-negative cUTI.
This SLR was undertaken according to the principles of systematic reviewing embodied in the Cochrane handbook and guidance published by the Centre for Reviews and Dissemination (CRD), and included all relevant RCTs between January 2008 and December 2019. The protocol was registered on the PROSPERO database (CRD42018087699).

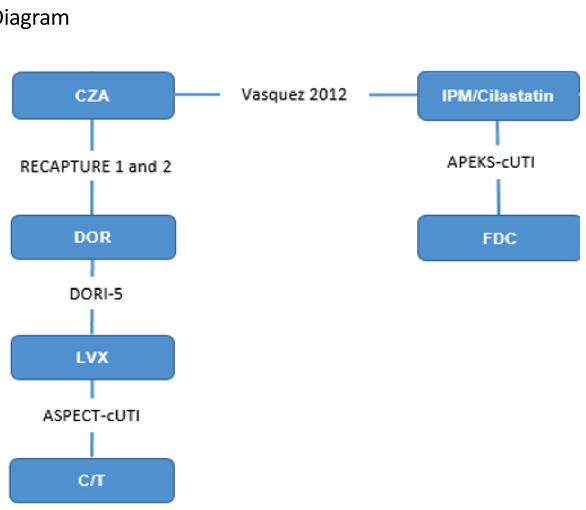
The population of interest was hospitalised adult patients with gram-negative cUTI. Comparators were defined broadly and searches were conducted in multiple databases according to a pre-specified search strategy. 16 RCTs were identified that assessed treatment of patients with cUTI. These formed a series of disconnected networks including Carbapenem sensitive (Carb-S) and Carbapenem non-sensitive (Carb-NS) pathogens.

The following outcomes were considered:
- Microbiological eradication (ME) at test of cure (TOC) and sustained follow-up (SFU)
- Clinical cure (CC) at test of cure (TOC)
- Adverse events (AEs) and discontinuation due to adverse events

Following the systematic review a feasibility assessment was conducted to determine the studies that would be suitable for the NMA, which excluded studies that only included Carb-NS pathogens. Due to heterogeneity in time reporting, evidence networks were constructed for separate timepoints including time of cure (TOC) as defined in the study and sustained follow up (SFU).

A total of 5 studies, 6 interventions and 2,349 randomised patients were included in the final analysis. Interventions included in the study were cefiderecol (FDC), imipenem-cilastin (IPM-CIL), ceftazidime-avibactam (CZA), doripenem (DOR), levofloxaxin (LVX) and ceftolozane-tazobactam (C/T). Trials included relevant differences in pathogen distributions, but not in terms of species included, being predominantly infections caused by Enterobacterales, and *Pseudomonas aeruginosa* and very few infections caused by *Acinetobacter baumannii.* The patient population presented some clinically relevant differences across trials, which were not adjusted for the NMA. The overall network diagram for the analysis is shown in Figure 2.

Figure 2: 'Overall' Network Diagram



Legend: CZA – ceftolozane/tazobactam; IPM – Imipenem; DOR – Doripenem; FDC – cefiderocol; C/T – ceftazidime/avibactam; LVX - levofloxacin

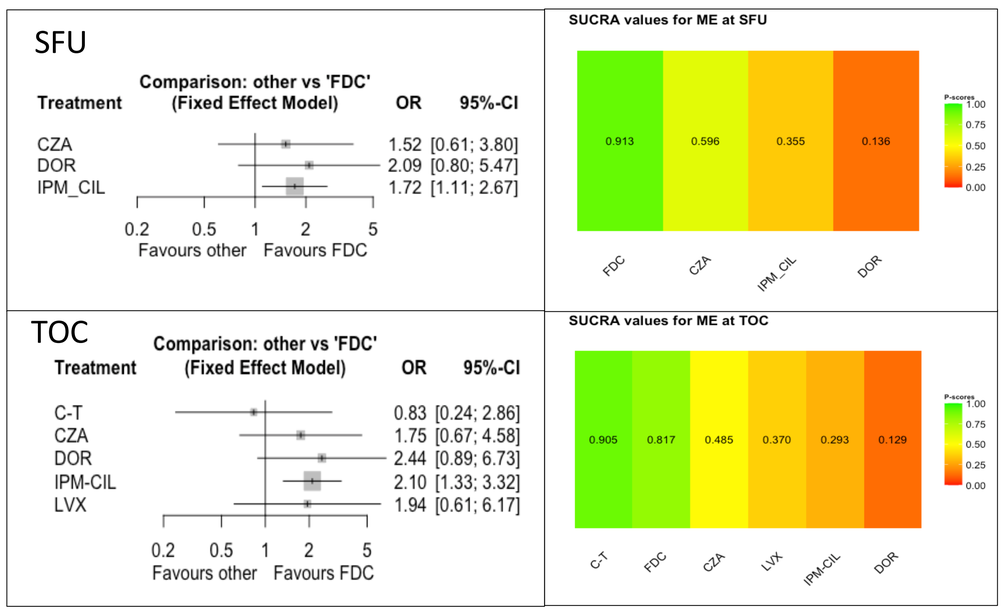
It should be noted that the network diagram in Figure 1 represents a 'best case scenario' network based on all of the RCT evidence and comparators identified and, depending on reporting in individual RCTs some outcomes were associated with fewer RCTs and comparators.

All analyses were conducted in R using the Netmeta package and code designed by the NICE decision support unit (DSU). Analyses were presented in terms of forest plots using odds ratios and SUCRA values. Due to the structure of the evidence networks (no cases where multiple studies make the same comparison) fixed effects models were used in all cases. All treatments were compared to FDC and confidence intervals were calculated at the 95% level for all treatment contrasts.

Results

Overall, there were numerical differences (especially in endpoints at SFU favouring CFDC), but all treatments showed similar efficacy and safety, with exception of higher ME rate at TOC for cefiderocol vs imipenem, also observed at SFU, consistent with the data from the individual clinical trial. Forest plots and SUCRA diagrams for the primary outcome of this analysis (ME at TOC and SFU) are shown in Figure 3.

Figure 3: Forest plots (left) and SUCRA diagrams (right) for ME and SFU (>1 favours FDC in forest plot)



Legend: sustained follow-up (SFU), Test of cure (TOC) cefiderecol (FDC), imipenem-cilastin (IPM-CIL), cefdazimine-avibactam (CZA), 'doripenem (DOR), levoflaxin (LVX) and ceftazalone-tazobactam (C/T)

The forest plots in Figure 3 show that there are no statistical significant difference between cefiderocol and comparators, except vs imipenem/cilastatin, which is consistent with the results observed in the clinical trial APEKS cUTI[2]. From the forest and SUCRA plots that cefiderocol was the most efficacious treatment for microbiological eradication at SFU and C/T was the most efficacious at TOC, followed by FDC.

Results for Clinical Cure outcome (at TOC and SFU), and 'any' AEs and AEs leading to discontinuations are shown in Table 1 and Table 2 respectively. Similar to ME results, there are no statistical significant differences, but in the SUCRA analysis FDC was the most efficacious treatment at SFU.

Table 1- Clinical cure results

Comparator	Clinical Cure			
	SFU		TOC	
	OR (95% CI)*	SUCRA	OR (95% CI)*	SUCRA
CZA	1.17 (0.35 to 3.96)	0.62	0.87 (0.19 to 3.89)	0.59
DOR	1.3 (0.36 to 4.64)	0.44	0.86 (0.18 to 4.14)	0.59
IPM-CIL	1.67 (1.00 to 2.79)	0.21	1.25 (0.64 to 2.47)	0.28
FDC	Reference	0.74	Reference	0.53
>1 Favours FDC; *Statistically significant				

Table 2- Safety results

Comparator	Safety			
	Any adverse event		Withdrawal	
	OR (95% CI)*	SUCRA	OR (95% CI)*	SUCRA
CZA	0.99 (0.42 to 2.33)	0.57	1.44 (0.56 to 3.69)	0.87
DOR	1.25 (0.51 to 3.05)	0.89	-	-
IPM-CIL	0.65 (0.44 to 0.96)	0.16	0.76 (0.40 to 1.45)	0.12
FDC	Reference	0.64	Reference	0.51
<1 Favours FDC; *Statistically significant				

It can be seen from Table 2 that no specific trends were identified for safety and no results were statistically significant.

Discussion

This analysis was designed to assess the efficacy and safety of current treatments for Gram-negative infections of the urinary tract using data identified in the literature, via indirect treatment comparison (ITC). Following assessment of similarity of trials and outcome definitions, the interventions assessed were cefiderecol (FDC), imipenem-cilastin (IPM-CIL), ceftazidime-avibactam (CZA), doripenem (DOR), levoflaxin (LVX), ceftolozane-tazobactam (C/T).

Overall, results showed no statistically significant difference between FDC and comparators, with the exception of FDC vs IPM-CIL in the analysis of microbiological eradication at TOC and follow up for FDC vs IPM-CIL, favouring FDC, which is consistent with the results of APEKS cUTI study. A SUCRA analysis also showed that FDC had the highest probability of being more effective at follow up for microbiological eradication and clinical cure outcomes. No specific notable trends were observed for adverse events with all odds ratios crossing the line of null effect. These results are expected given the non-inferiority design of the trials included.

This analysis is associated with some limitations. Due to the lack of data in this area, studies have been combined in evidence networks despite the presence of pathogen, clinical and study design heterogeneity. In the absence of patient level data it is not possible to quantify the extent to which this may induce bias in the analysis and results should therefore be interpreted in this context. Furthermore, availability and definition of analysis populations, outcomes and timelines (e.g. CC, ME at FU) varied across trials; thus, limiting the ability to include evidence and introducing uncertainty in effect estimates. Due to the limited evidence network, often informed by a single trial, it was not possible to undertake scenario analysis to explore key elements of heterogeneity and maintain a network of evidence; therefore, a fixed effects model was used.

The inability to adjust for potential treatment effect modifiers, such as the distribution of patients with pyelonephritis, disease severity and causative pathogens may underestimate the benefit observed by interventions studied in more severe populations; i.e. the inclusion of patients with acute or uncomplicated pyelonephritis were restricted to 30% in APEKS-cUTI, but were more prevalent in the other studies.

Conclusion

Novel antibiotic treatment options are welcomed for Gram-negative cUTI infections, as bacterial resistance is a growing worldwide concern, particularly for carbapenem resistant pathogens.
This NMA, showed superiority of CFDC vs IPM-CIL in ME at TOC and FU, and similar efficacy and safety vs all other comparators, with numeric differences favouring CFDC for outcomes at SFU, supporting a role of cefiderocol for the treatment of Gram-negative cUTI.

However, these traditional methodologies for NMA, present significant limitations when applied for antimicrobials, which limit the ability to conduct reliable comparative data synthesis, and therefore may not reflect the full value of breadth of coverage that new therapeutic options bring for the treatment of MDR GN pathogens. As such results of such analyses should be interpreted with caution. It would be important to identify ways to overcome these challenges.

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