Reinforcement of an Antimicrobial Stewardship Task Force Aims at a Better Use of Antibiotics of Last Resort: the COLITIFOS Study

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Introduction

Physicians are facing a worldwide increase in multidrug-resistant (MDR) organisms. Eradication of such bacteria, including so called superbugs (XDR), may cause physicians to prescribe last-resort antibiotics. However, experience with these drugs is limited and few data are available.

The French National Agency for Medicines and Health Products Safety (ANSM) has recently listed 6 parenteral drugs of last resort considering gram-negative bacteria: colistin, tigecycline, carbapenems, fosfomycin, phenicols, and temocillin.

In an era of when carbapenem-sparing regimens are promoted, we conducted a study to evaluate their main alternatives which are known as antibiotics of last resort.

One major player in antibiotic stewardship is an infectious disease specialist (IDS) in antimicrobial therapy, especially in an era of dramatic increase of antimicrobial resistance.

Objectives

The aim of this study was to evaluate

(i) the microbiological findings and clinical data supporting such prescriptions,

(ii) if there were alternative agents and

(iii) the role of a remote IDS consultant on the good use of antibiotics of last resort.

Methods

Hôpital Raymond-Poincaré is a tertiary hospital specialized in neurological impairment with acute care facilities, 255 beds, including 43 beds in the adult ICU, and a 108-bed rehabilitation unit. Therefore, patients are frequently colonized by MDR organisms.

A before and after retrospective study was conducted from January 2008 to June 2016. Prescriptions of IV antimicrobials considered as last-resort antibiotics (colistin, fosfomycin, tigecycline and temocillin) were reviewed by 4 infectious disease specialists (according to microbiology results, susceptibility testing, clinical situation and alternative agents), while doses were analyzed by a pharmacist.

As a second step, the cohort was split before and after 2013 coinciding with the arrival of a referent in antimicrobial stewardship.

Results

	Antibiotic (International drug name)	N (%)
Monotherapy	Colistin	6
	Tigecyclin	2
	Temocillin	1
	TOTAL	**9 (11.7)**
Combination therapy with 2 antibiotics	Fosfomycin + carbapenem	9
	Fosfomycin + β-lactam	8
	Fosfomycin + glyco or lipopeptide	4
	Colistin + carbapenem	4
	Colistin + β-lactam	4
	Colistin + aminoglycoside	3
	Fosfomycin + fluoroquinolone	3
	Colistin + aztreonam	2
	Fosfomycin + aminoglycoside	2
	Tigecyclin + carbapenem	2
	Colistin + fluoroquinolone	1
	Fosfomycin + rifampin	1
	TOTAL	**43 (55.8)**
Combination therapy with 3 or more antibiotics	Colistin + aminoglycoside + carbapenem	6
	Fosfomycin + β-lactam + glyco or lipopeptide	4
	Fosfomycin + carbapenem + aminoglycoside	2
	Fosfomycin + β-lactam + aminoglycoside	2
	Colistin + glyco or lipopeptide + carbapenem	2
	Tigecyclin + carbapenem + glyco or lipopeptide	2
	Colistin + glyco or lipopeptide + aminoglycoside	1
	Colistin + rifampin + aminoglycoside	1
	Colistin + carbapenem + metronidazole	1
	Colistin + fosfomycin + aztreonam	1
	Colistin + aminoglycoside + β-lactam	1
	Fosfomycin + aminoglycoside + glyco or lipopeptide	1
	Tigecyclin + carbapenem + aminoglycoside	1
	TOTAL	**25 (32.5)**

Table 1. Types of prescribed antimicrobial therapies (N=77)

Variables	Before 2013 n (%)	After 2013 n (%)	p-value (alpha=0.05)
	Documentation of infections		
Microbiological findings	37 (77.1)	28 (96.5)	
Non-documented	11 (22.9)	1 (3.5)	**0.02**
	Susceptibility of micro-organisms		
Susceptible organism	14 (29.2)	2 (6.9)	
Non-susceptible organism	34 (70.8)	27 (93.1)	**0.02**
	Alternative regimen		
Possible alternative antibiotic	39 (81.2)	20 (69.0)	
No alternative	9 (18.8)	9 (31.0)	0.27
	Outcome		
Favorable outcome	33 (68.8)	25 (86.2)	
Failure/death	15 (31.2)	4 (13.8)	0.10
	Dose of antibiotic		
Appropriate doses	21 (43.8)	21 (72.4)	
Inappropriate doses	27 (56.2)	8 (27.6)	**0.02**
	Charlson Comorbidity Index (CCI)		
CCI <5	21 (43.8)	16 (55.2)	
CCI ≥5*	27 (56.2)	13 (44.8)	0.33
Total	**48**	**29**	**-**

*Cohort was divided according to CCI median equal to 5. Patients with a CCI scores ≥5 are considered as severe and fragile.

Table 2. Univariate analysis of factors which may have been impacted by the reinforcement of antibiotic task force. Variables are compared before/after 2013, using Fisher's exact test.

Discussion

Our study shows that after the reinforcement of the antimicrobial **stewardship task force**, prescriptions of antibiotics of last resort were far more concordant with the good use of antibiotics, considering **microbiology results (*P* = 0.02) and doses (*P* = 0.02).**

The post-prescription review was more efficient at leading to better use of last-resort antibiotics. It emphasizes the importance of teamwork with an IDS, a microbiologist, and a pharmacist to optimize the use of antibiotics.

IV fosfomycin was the most prescribed antimicrobial therapy, followed by colistin. This can be explained by the high rate of bone and joint infections, which benefit from the good bone diffusion of IV fosfomycin, and the few resistant *P. aeruginosa* strains (as shown in Tables 1 and 2).

Due to a low rate of adverse events observed in the study, we cannot conclude whether antibiotics of last resort were less safe than other regimens. But the small report of adverse events suggests that drugs of last resort cannot be responsible for causing adverse effects. Moreover, most of the prescriptions were inadequately dosed, especially colistin, which may have decreased their toxicity.

Conclusion

The reinforcement of the antimicrobial stewardship task force aims at a better use last resort antibiotics for MDR and XDR organisms, lack of alternative regimens, and doses. Such contribution is most wanted in a an era of development of resistance.

45% of patients received inadequate doses which may contribute to treatment failure and emergence of resistance and possibility underestimate adverse events.

Further studies concerning antibiotics of last resort are required to confirm these findings, in an era where the lack of development of new drugs which contributes to the current use of last resort antibiotics.

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