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Review

Role of antimicrobial restrictions in bacterial resistance control: a systematic literature review

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SUMMARY

Background: Antimicrobial stewardship is considered as one of the most fundamental aspects of bacterial resistance control. Among the multitude of initiatives, restrictive strategies have been widely practiced in hospital settings. However, data concerning their potential effectiveness have not been methodically collected and evaluated to date.
Aim: To identify, collect and evaluate the available evidence regarding the impact of restrictive policies on bacterial resistance in hospital settings.
Methods: A systematic literature review was conducted using the PubMed/Medline, Embase, Global Health and CINAHL Plus databases.
Findings: In total, 5555 papers were retrieved in the search process, and 29 studies were included in the final analysis. There were no randomized studies, and the inherent limitations of the observational designs employed impede the deduction of safe conclusions. Seemingly beneficial interventions encompass the restriction of broad-spectrum cephalosporins in favour of beta-lactam/lactamase inhibitor combinations as well as the restriction of fluoroquinolones. Antimicrobial restrictions might also play a role in the control of vancomycin-resistant enterococci, while carbapenem stewardship in the form of the preferred use of ertapenem did not produce the anticipated results. Complex restrictions are not offered for informative comparative analyses. Hospital-wide policies could perhaps be superior to those confined to high-risk departments. Carbapenem-resistant *Acinetobacter baumannii* might be difficult to control through solely formulary interventions.
Conclusion: The presumably effective restrictive strategies rely mainly on inadequately tested hypotheses and low-quality evidence. Therefore, systematic, high-quality research is needed to confirm and expand comprehension of the subject so that the most successful policies are employed in the field.

Introduction

Antibiotic resistance has risen to among the 10 most critical public health threats worldwide, and is currently believed to be closely associated with the long-term exercise of inappropriate prescribing practices [1]. Antimicrobial stewardship has come into play as a multi-faceted set of approaches which aim to streamline antibiotic use by intervening on the chosen drug, the dose and the duration of treatment, with the ultimate goal of optimizing patient outcomes including an anticipated decrease in resistance rates [2]. Approaches are broadly divided into those aiming to persuade the prescribers to change

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Table I
Catalogue of the included studies further subgrouped by restriction type

Authors	Restriction type	Substitute agents	Setting	Study design	Results
Du *et al.* [11] 2003	Restriction and pre-authorization of 3GC (cefotaxime, ceftriaxone, ceftazidime)	4GC or carbapenems (not further clarified)	ICU, China	Before-and-after	Decrease in 3GC- and cefepime-resistant *E. coli* and *K. pneumoniae* percentages Insignificant decrease in ESBL *K. pneumoniae* and *E. coli* percentages (P=0.07) Insignificant changes for imipenem-resistant *K. pneumoniae* and *E. coli* percentages Insignificant changes for cephalosporin- and imipenem-resistant *A. baumannii* and *P. aeruginosa* percentages
Lipworth *et al.* [8] 2006	Restriction of ceftriaxone and ceftazidime	Ampicillin-sulbactam ± gentamicin instead of ceftriaxone Cefepime instead of ceftazidime	Hospital-wide, USA	Before-and-after	Hospital A: decrease in ESBL and increase in MRSA incidence rates; increase in ampicillin-sulbactam-resistant *K. pneumoniae* percentages; insignificant changes for gentamicin and no data for cefepime susceptibilities; increase in fluoroquinolone-resistant *P. aeruginosa* and *E. coli* percentages Hospital B: insignificant decrease in ESBL incidence rate (22% reduction P=0.36); no susceptibility data available pre-restriction for other agents
Brahmi *et al.* [9] 2006	Restriction and pre-authorization of ceftazidime	Piperacillin-tazobactam	ICU, Tunis	Before-and-after	Decrease in ESBL *K. pneumoniae* percentages post-restriction and no significant changes for ESBL *E. coli* or *P. mirabilis* Decrease in ceftazidime-resistant *A. baumannii* percentages post-restriction and no significant changes for piperacillin-tazobactam or carbapenems Decrease in piperacillin-tazobactam-resistant *P. aeruginosa* percentages during and post-restriction and no significant changes for ceftazidime or carbapenems
Araujo *et al.* [38] 2007	Restriction of cefepime as second-line empirical treatment	Piperacillin-tazobactam	NICU, Brazil	Before-and-after	Higher probability of remaining free of MDR Gram (-) colonization or infection during cefepime restriction in comparison with pre- and post-restriction era
Bassetti *et al.* [12] 2009	Restriction and pre-authorization of cephalosporins	Fluoroquinolones or piperacillin-tazobactam	ICU, Italy	ITS	Decrease in levels of MRSA percentages Increasing trend of ceftazidime-susceptible *K. pneumoniae* percentages Unclear significance of susceptibility changes to ciprofloxacin and piperacillin-tazobactam for *K. pneumoniae* and *P. aeruginosa*
Murki *et al.* [10] 2010	Restriction of cephalosporins	Ampicillin-sulbactam + amikacin for empirical	NICU, India	Before-and-after	Decrease in ESBL percentages Decrease in ciprofloxacin-resistant Gram (-)

		treatment Quinolones, piperacillin-tazobactam or carbapenems for definitive treatment			bacteria percentages Insignificant changes for amikacin or ampicillin-resistant Gram (-) bacteria percentages Insignificant decrease in piperacillin-tazobactam-resistant Gram (-) bacteria percentages (P=0.08) No data for carbapenems
Freedman *et al.* [16] 2007	Restriction and pre-authorization of fluoroquinolones Educational campaign to avoid treating asymptomatic bacteriuria and wait (if possible) for culture results	Oral amoxicillin ± gentamicin, cephalexin, nitrofurantoin or fosfomycin Amoxicillin ± clavulanate, macrolides, doxycycline or co-trimoxazole for respiratory infections Amoxicillin-clavulanate or co-trimoxazole plus metronidazole for diverticulitis Ceftriaxone + gentamicin for sepsis	Hospital-wide (psychiatric), USA	Before-and-after	Increase in fluoroquinolone-, ampicillin- and co-trimoxazole-resistant *E. coli* percentages pre-intervention Insignificant decrease in fluoroquinolone-resistant *E. coli* percentages during restriction Insignificant changes for nitrofurantoin-, gentamicin-, tetracycline-, co-trimoxazole- and ceftazidime-resistant *E. coli* percentages during intervention; no data available for the rest
Charbonneau *et al.* [6] 2006 Parienti *et al.* [7] 2011	Restriction of fluoroquinolones	Beta lactams ± aminoglycosides, tetracyclines, macrolides, rifampicin, co-trimoxazole or clindamycin	Hospital-wide, France	Controlled before-and-after ITS	Decreasing trends of MRSA percentages during restriction at intervention hospital; reversal in trend after fluoroquinolone re-introduction; lower MRSA incidence rate in comparison with control hospitals No change for fluoroquinolone-resistant Gram (-) bacteria percentages at intervention hospital No data available for susceptibility changes to substitute agents
Aldeyab *et al.* [17] 2012	Restriction and pre-authorization of fluoroquinolones	Not clarified	Hospital-wide, Ireland	ITS	Decrease in fluoroquinolone-resistant ESBL percentages associated with decrease in ciprofloxacin use Decrease in ESBL incidence rates associated with decrease in ciprofloxacin use
O'Brien *et al.* [18] 2015	Restriction of fluoroquinolones	Broad-spectrum beta-lactams or aminoglycosides	Hospital-wide, USA	Before-and-after	Positive association between ciprofloxacin use and urinary *E. coli* percentages non-susceptible to ciprofloxacin after controlling for non-significant variables Negative association of ceftriaxone use with urinary *E. coli* percentages non-susceptible to ciprofloxacin No other associations of key antibiotic classes with susceptibility to ciprofloxacin

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Table I (*continued*)

Authors	Restriction type	Substitute agents	Setting	Study design	Results
Pakyz *et al*. [27] 2009	Retrospective comparison of the incidence rate of carbapenem-resistant *P. aeruginosa* in hospitals with and without active carbapenem restriction	Not clarified	Hospital-wide, USA	Retrospective cohort	Carbapenem-resistant *P. aeruginosa* incidence rates (but not percentages) lower in hospitals with restriction
Yoon *et al*. [21] 2014	Restriction and pre-authorization of group 2 carbapenems	Ertapenem for ESBL infections	Hospital-wide, South Korea	Before-and-after	Increase in CRAB percentages and comparable incidence rates during restriction Positive correlation between group 2 carbapenems and CRAB percentages but no correlation for ertapenem Increase in ESBL *K. pneumoniae* and ESBL *E. coli* percentages during restriction Insignificant changes for carbapenem-resistant *P. aeruginosa*
Rodriguez-Osorio *et al*. [22] 2015	Restriction and pre-authorization of group 2 carbapenems Exclusion of ticarcillin-clavulanate and cefepime from hospital formulary	Ertapenem for ESBL infections Piperacillin-tazobactam instead of ticarcillin-clavulanate Amoxicillin-clavulanate instead of cefepime	Hospital-wide, Mexico	ITS	Increasing trends of carbapenem-resistant *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* percentages Increasing trends of 3GC-resistant *E. coli*, *K. pneumoniae* and *A. baumannii* percentages No association between ertapenem use and resistance of index organisms in multi-variate analysis
Garcia-Martinez *et al*. [39] 2016	Post-prescription review and approval of linezolid use	Not clarified	Hospital-wide, Spain	Before-and-after	Decrease in relative risk of linezolid-resistant *Enterococcus faecalis* and coagulase-negative staphylococcus attributed to reduced linezolid consumption in adjusted model
Sarma *et al*. [29] 2015	Restriction of cephalosporins and fluoroquinolones	Piperacillin-tazobactam instead of intravenous cefuroxime Nitrofurantoin or trimethoprim instead of oral cefalexin for UTI Piperacillin-tazobactam plus gentamicin instead of cefuroxime for complicated or nosocomial UTI Piperacillin-tazobactam instead of levofloxacin for severe community-acquired pneumonia Tigecycline for	Hospital-wide, USA	ITS	Decrease in level of ciprofloxacin-resistant urinary ESBL *E. coli* percentages No significant change in trends Correlation between ciprofloxacin resistance in ESBL *E. coli* urinary isolates and total number of ESBL *E. coli* (R^2=0.78) Correlation between ciprofloxacin use and fluoroquinolone resistance in Enterobacteriaceae urinary isolates (R^2=0.9)

		penicillin-allergic patients			
Boel *et al.* [30] 2016	Restriction and exclusion of cephalosporins and fluoroquinolones from hospital formulary	Penicillin G, ampicillin or dicloxacillin with gentamicin	Hospital-wide, Denmark	Controlled ITS	Reversal from an increasing to a decreasing trend for cefuroxime-resistant *E. coli* isolates only at the intervention hospital Reversal from an increasing to a decreasing trend for ciprofloxacin-resistant *E. coli* at the intervention hospital and reduction in slope at the control hospital
Aldeyab *et al.* [40] 2014	Restriction and pre-authorization of 2GC, 3GC, fluoroquinolones and clindamycin Monitoring of amoxicillin-clavulanate and macrolides	Not clarified	Hospital-wide, Ireland	ITS	Negative change in MRSA trend (remaining significant after adjusting for use of alcohol hand rub) No significant change in MRSA level
Rahal *et al.* [41] 1998	Restriction and pre-authorization of 3GC, ciprofloxacin and imipenem (authorization beyond single dose administration already in place, ICU, paediatrics excluded for 72 h)	Ampicillin-sulbactam, piperacillin-tazobactam, co-trimoxazole, doxycycline, ofloxacin, gentamicin, tobramycin, amikacin, oxacilllin, erythromycin, clindamycin or vancomycin	Hospital-wide, USA	Before-and-after	Reduction in ESBL incidence rates hospital-wide Increase in imipenem-resistant *P. aeruginosa* incidence rates hospital-wide and in ICUs
Petrikkos *et al.* [42] 2007	Restriction and pre-authorization of 3GC, 4GC, carbapenems, fluoroquinolones and aztreonam as empirical treatment	Piperacillin-tazobactam	Hospital-wide, Greece	Before-and-after	Decrease in 3GC and cefepime-resistant *K. pneumoniae* percentages No significant changes for piperacillin-tazobactam-resistant *K. pneumoniae* percentages No significant changes for *E. coli*
Quale *et al.* [31] 1996 Landman *et al.* [32] 1997	Restriction and pre-authorization of 3GC, vancomycin and clindamycin	Piperacillin-tazobactam or ampicillin-sulbactam instead of 3GC	Hospital-wide, USA	Before-and-after	Decrease in MRSA and ceftazidime-resistant *K. pneumoniae* incidence rates; correlation between 3GC use and those incidence rates Increase in cefotaxime-resistant *A. baumannii* incidence rates Increase in ceftazidime-susceptible *P. aeruginosa* percentages but not incidence rates Decrease in mean monthly VRE numbers; lower percentage of colonized patients between point-prevalence studies pre- and post-intervention Positive correlation between cefotaxime use and VRE numbers

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Authors	Restriction type	Substitute agents	Setting	Study design	Results
Lautenbach *et al.* [33] 2003	Restriction and pre-authorization of vancomycin, ceftriaxone and ceftazidime	Ampicillin-sulbactam ± gentamicin instead of ceftriaxone Cefepime instead of ceftazidime	Hospital-wide, USA	Before-and-after	Increase in VRE percentages Positive correlation between annual clindamycin use and annual VRE prevalence
Lima *et al.* 2009 [23] Oliveira *et al.* 2011 [24] Lima *et al.* 2011 [25]	Restriction and pre-authorization of group 2 carbapenems, cefepime and vancomycin	Teicoplanin plus amikacin instead of vancomycin plus cefepime for surgical site infections Ertapenem for ESBL infections	Hospital-wide, Brazil	Before-and-after	Decrease in imipenem-susceptible and increase in gentamicin-susceptible *A. baumannii* percentages No change for *P. aeruginosa* susceptibility to carbapenems Increase in ciprofloxacin-susceptible Enterobacteriaceae percentages
Sáez-Llorens *et al.* [43] 2000	Restriction and pre-authorization of 3GC, imipenem, ciprofloxacin, piperacillin and vancomycin Exclusion of gentamicin from hospital formulary Adherence to the recommended duration of treatment	Not clarified	Hospital-wide, Panama	Before-and-after	Increase in cefotaxime- and gentamicin-susceptible *K. pneumoniae* percentages Increase in piperacillin-susceptible *A. baumannii* and *P. aeruginosa* percentages No other significant changes
Cook *et al.* [44] 2004	Restriction and pre-authorization of vancomycin (oral), linezolid and amikacin Post-prescription review and approval of fluoroquinolones, cephalosporins, carbapenems, clindamycin, ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, vancomycin (intravenous) and tobramycin	Not clarified	Hospital-wide, USA	Before-and-after	Increase in MRSA percentages in non-ICU settings Decrease in MRSA percentages in the ICU No significant changes for other sentinel micro-organisms
Altunsoy *et al.* [45] 2011	Restriction and pre-authorization of piperacillin-tazobactam, ticarcillin-clavulanate, glycopeptides and carbapenems Post-prescription review	Not clarified	Hospital-wide, Turkey	Before-and-after	No significant susceptibility changes for sentinel micro-organisms

	and approval of parenteral fluoroquinolones, 3GC, 4GC, amikacin and netilmicin				
Regal *et al.* [46] 2003	Post-prescription review and approval of amikacin, aztreonam, azithromycin, clarithromycin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, carbapenems, piperacillin-tazobactam and tobramycin	Not clarified	Hospital-wide, USA	Before-and-after	Decrease in ceftazidime-, piperacillin-, imipenem- and aztreonam-resistant *P. aeruginosa* percentages No significant changes for ciprofloxacin- and tobramycin-resistant *P. aeruginosa* percentages
Wu *et al.* [47] 2015	Post-prescription review and approval of 2GC, 3GC, 4GC, broad-spectrum penicillins, fluoroquinolones, carbapenems and glycopeptides	1GC, penicillin derivatives, aminoglycosides, macrolides or clindamycin	Hospital-wide, Taiwan	Before-and-after	Increase in overall susceptibilities of Gram (-) and Gram (+) bacteria
Ma *et al.* [34] 2016	Post-prescription review and approval of carbapenems, glycopeptides, linezolid, daptomycin and tigecycline Strict targets regarding antimicrobial use and financial penalties to non-compliant departments	Not clarified	ICU, USA	Before-and-after	Decrease in MDR percentages on ICU admission and ICU discharge Decrease in MDR percentages in patients transferred to ICU directly from the emergency room, surgery and internal medicine departments Positive correlation between monthly antibiotic consumption and monthly MDR isolation rates on ICU admission No correlation between ICU antibiotic consumption and MDR isolation rates on ICU discharge No correlation between carbapenem use and CRAB isolation rates on ICU admission No correlation between ICU carbapenem consumption and CRAB isolation rates on ICU discharge
Lai *et al.* [35] 2016	Retrospective comparison of: One hospital with active restriction and pre-authorization of broad-spectrum antimicrobials	Not clarified	Hospital-wide, Taiwan	Retrospective cohort	Increasing trend for piperacillin-tazobactam-resistant *A. baumannii* percentages at hospitals B and C Increasing trend for CRAB percentages at hospitals A, B and C Decreasing trend for ciprofloxacin-resistant

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Table I (*continued*)

Authors	Restriction type	Substitute agents	Setting	Study design	Results
	(beta-lactam/beta-lactamase inhibitor combinations, 3GC, 4GC, glycopeptides, tigecycline, carbapenems and all fluoroquinolones with ICUs included One hospital with the same policy excluding ICUs One hospital with active post-prescription review and feedback policy				*P. aeruginosa* and *A. baumannii* percentages at hospital A Decreasing trend for carbapenem-resistant *P. aeruginosa* percentages at hospital A and increasing trend at hospital C Increasing trend for ESBL *E. coli* percentages at hospitals B and C and increasing trend for ciprofloxacin-resistant *E. coli* percentages at hospitals B and C

1GC, first-generation cephalosporin-; 2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; 4GC, fourth-generation cephalosporin; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ICU, intensive care unit; ITS, interrupted time series; ESBL, extended-spectrum beta-lactamase; MDR, multi-drug resistant; MRSA, meticillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci.
The information recorded encompasses the substitute agents post-restriction, the setting, the study design and a summary of the main results. A *P*-value <0.05 was considered as the statistical threshold of significance by all teams, and thus is recorded as such in the relevant results section.

their practices and those applying mandatory restrictions of particular antimicrobial classes [3]. Restrictive measures may either refer to mandatory antibiotic pre-authorizations or to post-prescription reviews and approvals within fixed periods of a few days. Although resistance control is allegedly one of the foremost stewardship goals, and antimicrobial restrictions have been widely practiced, the evidence with regard to presumptive effectiveness has not been evaluated thoroughly. The aim of this literature review was to systematically identify, collect and evaluate the available evidence specifically pertaining to the impact of restrictive stewardship policies on the incidence of resistant bacteria within hospital settings.

Methods

A systematic literature review was performed using the Medline/Pubmed, Embase, Global Health and CINAHL Plus databases. A broad search strategy was initially applied that intended to scope the available literature concerning associations between a wide range of antimicrobial stewardship interventions and bacterial resistance. For this purpose, the definitions provided by major organizations such as the Infectious Disease Society of America [4,5] and the Centers for Disease Prevention and Control (CDC) [3] were utilized. The applied search approach would warrant that most of the relevant information on the subject would be retrieved and examined. The search was restricted to papers written in the English language and was completed on 1st April 2017. Three main concepts were covered in the search string: antimicrobial stewardship and its constituent strategies, antimicrobial resistance and the inpatient context of the interventions:

1. (antimicrobial stewardship) OR (antibiotic stewardship) OR (audit "and" feedback) OR (restriction) OR (pre?authorization) OR (antibiotic combination*) OR (antimicrobial combination*) OR (antibiotic cycling) OR (antimicrobial cycling) OR (antibiotic rotation) OR (antimicrobial rotation) OR (antibiotic time?out*) OR (antimicrobial time?out*) OR (dose adjustment) OR (dose optimi#ation) OR (antibiotic mixing) OR (antimicrobial mixing) OR (antibiotic de?escalation) OR (antimicrobial de?escalation) OR (parenteral oral conversion) OR (intravenous oral conversion) OR (procalcitonin) OR (electronic alert*) OR (electronic system*) OR (computeri#ed alert*) OR (computeri#ed system*) OR (automat* stop order*)
2. Exp Drug Utilization
3. 1 OR 2
4. (antibiotic resistan*) OR (antimicrobial resistan*) OR (multi?drug resistan*) OR (bacterial resistan*) OR (bacterial susceptib*) OR (susceptib* phenotype*) OR (antibiotic susceptib*) OR (antimicrobial susceptib*)
5. 3 AND 4
6. (nosocomial OR hospital* OR in?patient OR intensive care OR ICU*)
7. 5 AND 6

In total, 5555 papers were retrieved in the process, and their abstracts were examined for relevance. Studies were considered for inclusion in this review if antimicrobial restrictions were the sole or a fundamental element of the applied policy. Due to the absence of robust randomized designs in the sample, widening the inclusion criteria was the only feasible

choice. Thus, the decision was made to include non-randomized studies, the vast majority of which were simple before-and-after studies. This was in view of their limitations, mainly the potential bias towards a positive outcome and their propensity for confounding, which should be taken into account during the interpretation of results. Studies which imposed very complex, multi-disciplinary approaches raised severe barriers to any meaningful comparative analysis, given that the effects of each element could not be distinctly evaluated from the rest, and were finally excluded. Simple before-and-after studies whose pre- and post-intervention periods lasted for <1 year each were also excluded to minimize the confounding effects of seasonality on resistance rates. In addition, studies which concurrently imposed new infection control practices, studies without parallel or historical cohorts for comparison, and studies which lacked any statistical processing of the data to show significance were also excluded.

Results

In total, 29 studies examining the impact of restrictive policies on bacterial resistance were identified. Distinct papers discussing interventions applied at the same setting during overlapping periods were considered together. The sample encompassed 20 simple before-and-after studies, one controlled before-and-after study, six interrupted time series (ITS) studies and two cohort studies. Charbonneau *et al*. and Parienti *et al*. examined a single intervention with two distinct approaches, controlled before-and-after and ITS, but it was counted as a controlled before-and-after study [6,7]. In terms of intervention type, six studies addressed the impact of cephalosporin, four the impact of fluoroquinolone, three the impact of carbapenem and one the impact of linezolid restriction. The remaining studies applied multiple concurrent restrictions. Six studies relied on a post-prescription review and approval model. The information recorded for each study is illustrated analytically in Table I.

Cephalosporin restriction

Broad-spectrum cephalosporin restriction was generally accompanied by improvements in relevant susceptibilities of Enterobacteriaceae, mainly *Klebsiella pneumoniae*, expressed either as a decrease in extended-spectrum beta-lactamase-producing (ESBL) [8–10] or third-generation cephalosporin (3GC) resistance rates [11,12]. The most popular substitute agents in the post-restriction era were penicillin-based combinations including piperacillin-tazobactam and ampicillin-sulbactam. Both combinations have good Gram-positive and Gram-negative coverage, while piperacillin-tazobactam is also effective against *Pseudomonas aeruginosa*, thus being suitable for empirical treatment in hospital settings. However, none of the teams adequately explained what they expected to achieve with the established policies in terms of resistance rates post-restriction. It is rational to assume, however, that the relevant papers examined the theoretical notion that ESBLs will be less likely to survive and establish infections on host tissues virtually deprived by much of the antagonistic susceptible microbial flora when penicillin/β lactamase-inhibitor combinations are preferably administered, due to the superior in-vitro activity of the latter against the aforementioned strains. It is worth mentioning that ticarcillin-clavulanate or amoxicillin-clavulanate were not preferred by any team, potentially due to their property to induce the overexpression of AmpC-cephalosporinase *in vitro* [13].

An alternative approach encompassed the preferred administration of carbapenems or cefepime post-restriction [11]. The rationale underlying this approach is also vague. In terms of resistance potential, the sole postulated advantage of cefepime is its superior in-vitro activity against AmpC-overexpressing Enterobacteriaceae, which are less common than ESBLs in clinical practice [14]. Regarding carbapenems, a rational assumption could probably be that cephalosporin-resistant Enterobacteriaceae through ESBL or AmpC- β lactamases remain susceptible to the particular class and will therefore not be selected during treatment. Nonetheless, carbapenems are considered as agents of last resort against multi-drug-resistant (MDR) pathogens. Thus, the collateral damage induced by the potential establishment of carbapenem-resistant strains should definitely be a concern. In addition, imipenem is a strong inducer of AmpC-cephalosporinase *in vitro*, which could compromise any expected effect at concentrations below the bactericidal level [14]. Present studies with their inherent design limitations do not indicate the onset of collateral damage [11] or do not examine that possibility at all [10]. Finally, it is unclear whether fluoroquinolones could be a preferred substitute choice given that the available information is scarce and poorly informative [10,12]. Furthermore, current recommendations warn against their widespread use for safety concerns; an issue which was not examined by the authors [15].

Fluoroquinolone restriction

Four studies addressed the impact of fluoroquinolone restriction on resistance patterns [6,7,16–18]. Three of them indicated that this could be beneficial in terms of Enterobacteriaceae susceptibility to the particular antimicrobial class even in ESBL populations [16–18], with significant correlations between the levels of fluoroquinolone use and fluoroquinolone susceptibility shown by two studies [17,18]. Those observations are supported by the main biological mechanism implicated in the onset of reduced fluoroquinolone susceptibility which encompasses chromosomally mediated mutations in the genes encoding DNA gyrases. During treatment with fluoroquinolones, DNA gyrases of reduced affinity to the drug can be selected in a stepwise process, which is therefore closely related to the extent of fluoroquinolone exposure [19]. The study by Charbonneau and Parienti *et al.*, on the other hand, examined the effect of fluoroquinolone restriction on the incidence of meticillin-resistant *Staphylococcus aureus* (MRSA) [6,7]. They showed a significant downward trend post-intervention, as well as lower MRSA rates in comparison with control settings. They suggested that the observed association could be attributed to the increased adherence of staphylococci on host tissues through overexpression of fibronectin-binding proteins and the eradication of protective microbial flora during treatment, both of which facilitate MRSA colonization [20]. Interestingly, they did not report any improvement in the susceptibilities of Gram-negative populations to fluoroquinolones, in contrast to the former findings. Finally, the issue of collateral damage was not adequately addressed

by any team, with just one study reporting resistance rates to some of the substitute agents [16].

Carbapenem restriction

Two teams instituted the mandatory use of ertapenem for ESBL infections and the pre-authorization of group 2 carbapenems for particular clinical indications [21,22]. In addition, Lima/Oliveira *et al*. launched a similar policy in the context of a wider restrictive intervention [23—25]. Although not explicitly formulated, the main hypothesis underlying those initiatives is that the preferred use of ertapenem for suspected or confirmed ESBL infections could stem the onset of carbapenem-resistant non-fermenters. Ertapenem is inactive against the latter strains and theoretically less likely to exert selective evolutionary pressure towards carbapenem-resistant non-fermenting isolates. However, laboratory experiments led to subsequent concerns that cross-resistance might actually take place, leaving physicians uncertain as to whether such an initiative could be ultimately beneficial [26]. None of the three studies showed an actual benefit, with the incidence of carbapenem-resistant *A. baumanni* (CRAB) and *P. aeruginosa* remaining unchanged, or even worsening, post-intervention. Nonetheless, Yoon *et al*. supported the preferred use of ertapenem due to the absence of a statistical correlation between ertapenem consumption and CRAB proportions. However, they did not conduct the aforementioned statistical analysis for incidence rates, which are generally considered as more reliable indicators, despite the availability of the relevant data in their study [21]. Finally, Pakyz *et al*. retrospectively compared cohorts of hospitals with and without active carbapenem control programmes without, however, delineating on the policy elements, and suggested that controlled use might reduce the incidence of carbapenem-resistant *P. aeruginosa* [27].

Multiple restrictions

Fourteen studies examined the effects of multiple restrictions on resistance patterns in various sentinel microorganisms. However, the multitude of concurrent interventions and the variety of indicators measured impede any effort to compare and synthesize results, thus making it difficult to draw any conclusions. Such difficulties in policy evaluation are possibly one of the reasons why very complex strategies are also discouraged by CDC [28]. However, there are some points arising from the existing data which are noteworthy.

Two teams chose to concurrently restrict cephalosporins and fluoroquinolones. Sarma *et al*. used ciprofloxacin resistance as an indicator, and showed a decrease in levels of ciprofloxacin-resistant ESBLs as well as statistical correlation between ciprofloxacin use and ciprofloxacin-resistant Enterobacteriaceae [29]. This is in line with the results by Aldeyab [17] and O'Brien *et al*. [18] regarding solitary fluoroquinolone restriction. Boel *et al*. showed a reversal from an increasing to a decreasing trend for both cefuroxime- and ciprofloxacin-resistant *Escherichia coli* post-intervention [30].

Two studies on vancomycin-resistant enterococcus (VRE) control were performed by the Quale/Landman and Lautenbach teams [31—33]. The former substituted 3GC for piperacillin-tazobactam and restricted vancomycin as well as clindamycin, resulting in a reported reduction in nosocomial VRE numbers. The latter solely controlled 3GC and vancomycin, with poor results. Enterococci are intrinsically resistant to all three antimicrobial classes; this might explain the inconsistency given that Lautenbach *et al*. also presented a positive correlation between clindamycin use and VRE rates.

Ma *et al*. instituted a hospital-wide post-prescription review and approval policy for broad-spectrum and second-line antibiotics, and imposed strict targets with financial penalties for non-compliant departments [34]. They found a radical decrease in MDR incidence on intensive care unit (ICU) admission as well as ICU discharge which correlated with hospital-wide and not ICU antibiotic consumption. The latter underlines the importance of not confining the instituted policies solely in high-risk departments. Interestingly, no such correlation was deduced by the same team between carbapenem consumption and CRAB. This is in accordance with the results by Yoon [21], Rodriguez-Osorio [22], Lima/Oliveira [23—25] and Lai *et al*. [35], who generally failed to show any benefits on the incidence of CRAB through formulary interventions.

Discussion

Antimicrobial stewardship has been emphatically stressed as a fundamental tool to tackle bacterial resistance in health care. Among the multitude of initiatives, restricting the use of antibiotics viewed as of a high-risk profile probably constitutes one of the most widely practiced interventions. Thus, it was rather surprising that the available evidence regarding the effectiveness of such strategies relies on low-quality research, basically observational studies that most often use historical cohorts as controls. Obviously performing a cluster randomized controlled trial is complex and logistically difficult to materialize. Nonetheless, the public health importance of the issue warrants such investments to reach safe conclusions of what can be successful. Furthermore, it is necessary to establish a common systematic approach with regard to the variables and indicators that should be measured to evaluate effectiveness. This would allow comparison and synthesis of the study findings and would uncover the obvious direct effects as well as the possibly inconspicuous collateral damage incurred by the instituted policies. For now, a basic assumption has been made to proceed to interpretation of the available data, that a particular restriction would lead to a significant reduction in relevant antibiotic use and a shift towards the use of substitute agents with analogous changes in evolutionary pressures. However, many teams seemed to ignore that there is an obvious risk of 'squeezing the balloon'. They either did not record resistance rates in substitute agents or did not mention the latter at all. Furthermore, there was often a lack of concrete reasoning to account for the stewardship initiatives employed. It is worth mentioning that agents restricted in a setting are used as substitutes in another on the grounds of vague hypotheses and a seemingly absent theoretical background to support those clinical decisions in relevant papers.

Given the aforementioned limitations and in view of the available data, one could say that restricting broad-spectrum cephalosporins in favour of penicillin/β-lactamase inhibitor combinations was consistently associated with improvements in relevant susceptibilities. Whether this is a true effect remains to be answered by more rigorous study designs. If this is the case, however, it would be interesting to examine the

eventual superiority in terms of resistance potential of the lately launched promising agents, ceftolozane-tazobactam and ceftazidime-avibactam. The latter similarly rely on β-lactamase inhibitors but are further active against particular carbapenem-resistant Gram-negative strains. Fluoroquinolone restriction might also be beneficial in the control of fluoroquinolone-resistant Enterobacteriaceae, including fluoroquinolone-resistant ESBLs as well as MRSA populations. The results obviously suffer from the aforementioned limitations, and are moreover incomplete in terms of not examining the issue of possible collateral damage. Finally, carbapenem stewardship was seemingly unsuccessful, with CRAB appearing consistently robust against such policies. A reasonable explanation could lie in the environmental persistence of *Acinetobacter* spp. as well as its notorious capability to exploit multiple resistance mechanisms concomitantly [36,37]. Therefore, meticulous infection control could be the missing pivotal policy element to address the burden. Complex restrictions offered few opportunities for meaningful comparisons with exemption of the efforts to stem VRE by depriving the strains from a major selection advantage through restricting key inactive antimicrobial classes. Finally, there is some evidence that hospital-wide policies could be superior, a finding which could perhaps be related to a more drastic impact exerted on colonization pressures.

In conclusion, systematic, high-quality research is needed to adequately evaluate the role of restrictive policies in the successful control of bacterial resistance. Available data indicate that particular interventions might be beneficial, but a more thorough and methodical approach is necessary to confirm and expand our limited knowledge on this field of utmost public health importance.

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