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Systematic review of the effects of antimicrobial cycling on bacterial resistance rates within hospital settings

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Abstract

Aim

Antimicrobial resistance is an evolving phenomenon with alarming public health consequences. Antibiotic cycling is a widely known antimicrobial stewardship initiative which encompasses periodical shifts in empirical treatment protocols with the aim of limiting selective pressures on bacterial populations. We present a review of the evidence regarding the actual impact of antimicrobial cycling on bacterial resistance control within hospitals.

Methods

A systematic literature review was conducted using the PubMed/MedLine, Embase, CINAHL Plus and Global Health databases.

Results

A systematic search process retrieved a sole randomised study, and so we broadened inclusion criteria to encompass quasi-experimental designs. Fifteen studies formed our dataset including seven prospective trials and eight before-and-after studies. Nine studies evaluated cycling versus a control group and produced conflicting results whilst three studies compared cycling with antibiotic mixing, with none of the strategies appearing superior. The rest evaluated resistance dynamics of each of the on-cycle antibiotics with contradictory findings. Research protocols differed in parameters such as the cycle length, the choice of antibiotics, the opportunity to de-escalate to narrow-spectrum agents and the measurement of indicators of collateral damage. This limited our ability to evaluate the replicability of findings and the overall policy effects.

Conclusions

Dearth of robust designs and standardised protocols limits our ability to reach safe conclusions. Nonetheless, in view of the available data we find no reason to believe that cycling should be expected to improve antibiotic resistance rates within hospitals.

Introduction

Evolving bacterial resistance to antimicrobial agents, one of the ten most critical public health threats according to the World Health Organization, demands immediate action[1]. Antimicrobial cycling or rotation is among the multitude of initiatives tried to streamline antibiotic prescribing, and fall within the umbrella term of antimicrobial stewardship. Cycling or rotation involves scheduled shifts in empirical antibiotic treatment protocols, switching periodically between antimicrobial agents of similar spectrum. This practice is often adopted in high-risk settings such as Intensive Care Units and relies more or less on an intuitive perception that such scheduled rotations of antimicrobial agents could alter selective pressures on bacterial populations accordingly and thus stem the onset of resistant strains. The concept was probably further developed in the 1990's when Gerding et al reported improvements in aminoglycoside resistance rates as a result of changes in the type of predominant aminoglycoside use[2][3].

However, mathematical models have challenged the strategy's presumed effectiveness by predicting that interventions which favoured a more heterogeneous antimicrobial use would be more successful in bacterial resistance control[4][5][6]. According to a 2006 systematic literature review very few studies met quality criteria for inclusion and lack of rigorousness in study designs for those finally included was insufficient to draw safe inferences[7]. A meta-analysis following almost ten years later suggested potential benefits by the application of the particular strategy without, however, performing an in-depth evaluation of the included studies some of which, in our opinion, suffer from methodological limitations that should not be ignored[8]. Since then, the escalating spread of multidrug-resistant strains within clinical settings has increased research interest on antimicrobial stewardship including cycling and has led to the publication of several further relevant studies.

We aim to provide an updated systematic review and evaluation of the evidence with regard to the impact of antimicrobial cycling on the incidence of antibiotic-resistant bacteria within hospital settings. Our study is a composite element of a wider project with the objective to assess the effects of different antimicrobial stewardship initiatives on bacterial resistance rates which has led to the publication of two additional papers discussing the role of antimicrobial restrictions[9] and prospective audit with feedback[10].

Methods

Eligibility criteria

We sought to retrieve all studies of reasonable quality which assessed the impact of antimicrobial cycling strategies on the incidence of infection and/or colonization with antibiotic-resistant bacteria within hospital settings. The working definition we used for antibiotic cycling encompassed the rotation of at least two different empirical antimicrobial regimens for at least two cycles of fixed duration for each of them. Thus we excluded all studies which examined a single switching from one empirical antibiotic protocol to another without their repeated re-introduction into clinical practice.

Initial scoping review of the literature revealed the scarcity of randomised designs on the field. Therefore, we decided to broaden inclusion criteria by considering quasi-experimental designs including non-randomised trials, cohort, interrupted time-series, controlled before-and-after as well as simple before-and-after studies which constitute the main bulk of literature on the subject. However, we excluded simple before-and-after studies which examined cohorts followed for less than one year each, to minimise confounding due to seasonality and to facilitate comparability of results. We also excluded studies which combined changes in infection control practices or applied multidisciplinary interventions due to confounding and constraints on comparability. Studies which lacked historical or parallel cohorts for comparison were not included as interpretation is impossible without some kind of internal control or comparator. Data provided by grey literature such as congress papers and reports from governmental and non-governmental organizations were outside our scope due to lack of peer review. Finally, studies which did not apply suitable statistical methods to evaluate the significance of the reported results were also excluded as were case-control studies.

A main distinction from prior meta-research on the topic is the fact that we considered changes in infection control as well as the application of additional antimicrobial stewardship interventions as important confounding factors which should not be overlooked; this led to the exclusion of several papers which other reviews have included.

Information sources

The Medline/Pubmed, Embase, Global Health and CINAHL Plus databases were searched. The search was restricted to papers written in the English language and was completed on 1st April 2020. No other restriction was applied.

Search strategy

The present study was part of a wider project looking at all hospital-based interventions intended to limit antibiotic resistance. This used a broad search algorithm on the basis of definitions provided by major organizations: Infectious Diseases Society of America (IDSA), Center for Disease Prevention and Control (CDC)[11][12]. The search string covered three concepts, antimicrobial stewardship and its constituent strategies, antimicrobial resistance, and the hospital setting 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

Note: The aforementioned truncation symbols were applicable to the Medline and Global Health databases and were accordingly adjusted to the other databases. The subject heading "Drug utilization" maps the term antimicrobial stewardship in Medline and was not available in other databases.

Data collection and extraction process

The titles and abstracts of the studies retrieved during the search process were reviewed independently by the authors. If the abstract was deemed as relevant or this was unclear the citation was extracted to an automated citation manager for full-text access. After the initial scoping phase of the review, studies on antibiotic cycling were further grouped and examined together. Discrepancies between the reviewers during the data collection process were resolved via discussion. Data extraction from the final dataset was performed by the first author to a standardised table where information about the study design, the setting, the study protocol and the primary outcome (incidence of infection and/or colonization with antibiotic-resistant bacteria) was recorded (Table 1). We also recorded antimicrobial consumption and morbidity and/or mortality rates as secondary outcomes for a more thorough assessment of the observed findings.

Risk of bias assessment

Production of high-quality research on antimicrobial stewardship is challenging partly due to the inherent characteristics of the interventions which preclude blinding and limit options for even partial randomization. Cluster randomization is probably the most suitable study design but is often complex and logistically difficult to perform. Thus most research to date relies on quasi-experimental designs which are obviously more prone to selection bias and confounding but including those designs was the only feasible option.

The assignment of quality scores to assess the quality of individual studies has been used to a lesser extent lately because such scales are not reliable and cannot be validated. Thus, we decided to use the Cochrane collaboration's tool for assessing risk of bias for Randomised Controlled Trials (RCTs) as well as the Newcastle-Ottawa Scale for non-randomised studies mostly as guidance tools to search for and identify potential sources of bias and exclude those studies deemed as of being at a higher risk of bias.

Given that all but one of the retrieved papers were highly heterogeneous non-randomised studies we excluded those where the institution of multidisciplinary interventions, changes in infection control or inadequate follow-up periods would compromise the comparability of cohorts and jeopardise the validity of findings. The sole randomised study retrieved during the search process was a non-blinded cluster cross-over study. The lack of blinding could theoretically lead to some degree of referral bias but is on the other hand unavoidable due to the inherent characteristics of the intervention under study. Due to the high heterogeneity of our dataset, superiority of particular research designs would be taken into account in case of conflicting results and the need for a subsequent sensitivity analysis.

Results

Study selection

8,922 papers covering the period to 1st April 2020 were screened for relevance. Fifteen relevant studies formed our final dataset including seven prospective trials and eight simple before-and-after studies. Details of the study selection process are depicted in the flow diagram of Figure 1.

Study characteristics

Nine studies evaluated the effects of antibiotic cycling versus a control group[13][14][15][16][17][18][19][20][21]. Three papers compared antimicrobial cycling with antibiotic mixing[22][23][24], that is administering the scheduled antimicrobial agents on a successive patient basis. The last three assessed the resistance potential of each of the alternating on-cycle antibiotics, that is the variations in risk of antibiotic resistant infection and/or colonization during cycles of different predominant antibiotic use[25][26][27]. Fixed durations of each cycle ranged from one week to eight months. The rotating agents were piperacillin-tazobactam with cefepime in two cases[13][25] and fluoroquinolones with beta lactams in three cases[18][26][27]. The rest rotated the aforementioned agents with carbapenems and aminoglycosides in varying combinations. In some protocols de-escalation to suitable narrow-spectrum agents was permitted but in others it was not, with six teams proceeding to de-escalation in view of bacterial susceptibility results[16][17][19][23][24][27], five teams avoiding de-escalation to increase the on-cycle antimicrobial use[14][15][18][21][26] and four teams not clarifying their practices enough for their readers to be able to ascertain specifically what they did[13][20][22][25]. Four studies provided bacterial typing data to assist in the evaluation of cross-transmission dynamics[14][18][25][27]. Furthermore, methodologies differed as to whether surveillance cultures or cultures from clinically presumed infections, unit-wide or patient-specific, were recorded as indicators of resistance incidence (Table 1).

Antimicrobial cycling versus standard practice (control cohort)

Among those studies which compared an experimental with a control cohort there were seven simple before-and-after and two prospective trials. Seven of these provided data with regard to antimicrobial protocols in the control group[14][15][16][18][19][20][21] and two did not set out their standard practice[13][17]. Oddly, many studies fail to state any explicit

goal of their chosen intervention, but the available information suggests that the institution of an antimicrobial rotation policy aimed to increase heterogeneity of antimicrobial administration in the intervention group by utilising more antimicrobial classes of similar spectrum in a scheduled fashion. The results, however, appear rather conflicting.

In particular, if one takes into account bacterial susceptibilities to the rotated agents, apparently a straightforward indicator of the policy's effectiveness, four studies did not achieve any measurable success and five reported variable improvement (Table 1). The most noteworthy study in the group reporting negative findings is probably the trial conducted by Toltzis et al. The researchers reported higher colonization rates with resistant bacilli to any of the rotated antibiotics in the rotation arm with the results not reaching statistical significance ($p=0.09$). The study's main distinctive feature is the use of a contemporaneous control group, and its use of bacterial typing data facilitates interpretation of the available findings. In particular, no significant differences were observable even when only clonally discordant isolates were taken into account[14].

The group reporting positive findings encompassed two studies which observed an increase in *P. aeruginosa* susceptibility to one and two of the rotated agents respectively[17][18] and two studies which reported improvements in Extended-Spectrum Beta Lactamase (ESBL) incidence ($p<0.05$)[20][21].The latter used a rather small sample while none of the aforementioned seemingly successful studies utilized bacterial typing to investigate the clonal associations of bacterial isolates. Thus, the possibility that the observed findings could be a result of horizontal transfer of bacterial clones due to breaks in infection control was not explored as it was in the study conducted by Toltzis et al.

Nijssen et al observed lower colonization rates for ciprofloxacin-resistant isolates in the intervention group ($p<0.01$) but no significant changes for cephalosporin-resistant isolates ($p>0.05$)[18]. The authors also reported a highly homogeneous prescription of fluoroquinolones in the control arm and a radical reduction in ciprofloxacin administration in the intervention arm. The aforementioned radical reduction in fluoroquinolone use along with the main mechanism of fluoroquinolone resistance induction could potentially account for the observed results, a scenario which is further examined in the Discussion section.

Frequency of cycling did not appear to be associated with the possibility of positive or inconclusive outcomes as it varied widely in both groups. Furthermore, the fact that universal lack of randomization and blinding in this part of dataset would potentially predispose to some degree of selection and information bias in favour of more positive outcomes, and while no specific biases were evident, this inevitable contextual bias should be taken into account.

Antibiotic cycling versus mixing

Three studies assessed antimicrobial rotation compared to administering the agents on a successive patient basis to maximise antibiotic heterogeneity, a practice known as antibiotic mixing. Two of those, including one using the robust cluster-randomised cross-over design, observed no significant differences ($p=0.73$ and $p=0.29$ respectively)[23][24]. Jayashree et al reported lower resistance rates in both cycling and mixing periods compared to a three-month baseline period ($p<0.001$). The latter, however, was too short to be informative[24].

The third reported higher cefepime susceptibility rates for *P. aeruginosa* during cycling (p=0.01) but no further improvements[22]. De-escalation as well as combination therapy were permitted in two instances[23][24], and their allowability was not clarified in the third[22]. None of the teams used typing data to assess cross-transmission dynamics.

Resistance potential of the alternating antimicrobial agents during the application of cycling protocols

As for the remaining studies, Ginn et al cycled piperacillin-tazobactam with cefepime and found that cefepime showed to be a more important driver for the onset of bacterial resistance than piperacillin-tazobactam with the proportion of admissions complicated by resistant infections during cefepime cycles being more than twice as high (p<0.001)[25]. Van Loon et al cycled levofloxacin with cefpirome and piperacillin-tazobactam concluding that levofloxacin use was associated with higher levofloxacin-resistance rates (p=0.003), but cefpirome was seemingly not prone to the selection of cefpirome-resistant strains (p=0.85)[26]. Tsukayama et al rotated fluoroquinolones with piperacillin-tazobactam but did not find any significant correlations between the on-cycle antibiotic class and the probability of resistance onset (p>0.05). However, the authors report high use of off-cycle antibiotics which could potentially act as a confounding factor[27].

Assessment of collateral damage within the available dataset

Finally, all but two studies provided some data regarding the on- and off-cycle antimicrobial consumption during the experimental period, while seven studies measured variable indicators of the policy's potential collateral damage including morbidity and/or mortality rates reported by six studies[15][16][19][22][23][24]. None of these recorded worrying trends in intervention groups (p>0.05).

Discussion

Bacterial resistance to antimicrobial agents is an incessantly evolving phenomenon which threatens one of the greatest achievements of medical science, the effective treatment of infectious diseases. Overprescribing and suboptimal selection of antimicrobial agents are believed to have contributed to the acceleration of the selection of resistant strains. Thus antimicrobial stewardship has provoked the interest of the medical community as a multifaceted set of interventions which aim to optimise antimicrobial use and thus stem the onset of resistant bacterial strains.

Despite, however, the public health importance of this issue, there is a notable lack of standardised high-quality research on the field to provide definitive answers as to which, if any, initiatives are effective. We have already examined antimicrobial restrictions and audit with feedback in two papers that were recently published[9][10.] The absence of randomised models and the great heterogeneity in study protocols limited the ability to draw any firm conclusions on the aspects researched. It highlights the need for future high-quality, reproducible research better informed by the underlying science on the development of resistance. Standardisation in study design would increase the utility of clinical research in

this field, as meta-synthesis of studies would be possible, providing greater statistical power to detect and map the effects of intervening to try to reduce resistance, and guide clinicians.

The first systematic review on antibiotic cycling was published in 2006 by Brown et al[7]. Only four studies reportedly met their inclusion criteria and even those suffered from multiple methodological limitations which did not allow for the induction of any meaningful conclusion according to the reviewers. Three out of the four papers they included were excluded from our own dataset on quality grounds. This was either due to the combination of changes in infection control practices or the lack of a suitably standardised cycling protocol. A meta-analysis followed by zur Wiesch et al[8] almost ten years later suggesting that the application of antimicrobial cycling could be actually beneficial in bacterial resistance control. However, there are important issues arising if one evaluates critically the dataset concerned. Two out of the eleven papers included were treated as distinct studies although they referred to the same intervention applied within the same setting during overlapping periods, and the instituted multidisciplinary policy of concurrent antimicrobial restrictions along with cycling may have confounded the results of this study, which was the reason for exclusion from our own dataset. An additional example of unclear methodology is the paper by Smith et al which zur Wiesch et al listed among the successful interventions[19]. Smith et al cycled vancomycin with linezolid and compared the incidence of resistance with a baseline period of primary vancomycin use. No significant change with regard to vancomycin-resistant Enterococcus (VRE) was observed as a straightforward marker of the strategy's effectiveness, but nonetheless, a statistically significant decrease in methicillin-resistant *Staphylococcus aureus* was attributed to the institution of the research protocol although there is no firm pathophysiological mechanism to account for such a causal association as indeed was recognised by the authors of the original paper.

In our opinion, critical examination of the available literature on the potential efficacy of antimicrobial cycling gives an overall impression of rather limited success and a generalised problem with study quality commencing with study concept and research design. Research papers could be roughly divided to those which evaluated cycling versus a control group and produced conflicting results and those that compared cycling with mixing with none of the strategies appearing superior to the other. Lack of success becomes more evident if one takes into account the most rigorous studies conducted by Toltzis et al[14] as well as Van Duijn et al[23]both of which failed to record any favourable results comparing cycling with a control group and a mixing group respectively. The cluster randomised study by Van Duijn et al was published relatively recently and was not included in previous systematic reviews.

Fair interpretation of our data must take into account some core limitations which could influence results either way. One such limitation is the lack of standardization of antibiotic protocols across intervention and control groups of different studies, though a general tendency to increase heterogeneity of antibiotic administration in the experimental arms was observable. It is rational to assume that the relevant baseline practices would influence whether significant changes in antibiotic resistance patterns would be recorded post-intervention. A pertinent paradigm is probably provided by Nijssen et al who compared antibiotic rotation with a control group receiving fluoroquinolones in a highly homogeneous

manner. Fluoroquinolone resistance rates were decreased in the rotation arm, a trend not seen for cephalosporins. It is well-known that the main mechanism of fluoroquinolone resistance comprises point mutations in chromosomal DNA which are obviously particularly prone to selective pressures. Radical reduction in fluoroquinolone administration along with the main relevant mechanism of resistance could provide a likely explanation for the observed results further supported in the clinical literature after the application of restrictive fluoroquinolone strategies[9].

We cannot exclude the possibility that the potential for success could be pathogen-specific and depending on the monitoring protocol it could be possibly missed; a pathogen-specific effect has indeed been suggested by researchers in the past[8]. It is true that the majority of the available positive findings in our dataset relate to *P. aeruginosa*, but without more data it seems impossible to propose a hypothesis to account for such an observation.

Failure of antibiotic cycling to produce clear benefits is consistent with the theoretical predictions generated by many mathematical models that challenge its intuitively presumed efficacy. The aforementioned models assume that antibiotic mixing would be more effective via maximising heterogeneous antimicrobial use. This assumption was not confirmed in practice. Although there is high variability in research protocols and the overall quality of our data is far from sufficient to reach definite conclusions, the evolution of bacterial resistance is a complex process and the strategies tested may rely on an oversimplified model of how it may be manipulated. Antimicrobial agents of similar spectrum may possess totally different mechanisms of action, and thus may affect bacteria in different ways. In addition, infection control is hard to standardise, and confounding from this source could influence relevant studies dramatically.

At this point, it would be useful to discuss the third set of studies included in our review. The latter evaluated resistance dynamics of each of the on-cycle antibiotics during the application of antimicrobial cycling protocols. They provide little information as to the overall efficacy of cycling but could offer some ground for future research as to which agents are actually less prone to the selection of resistant strains. Ginn et al compared periods of predominant cefepime and piperacillin-tazobactam use and found that cefepime, a fourth-generation cephalosporin, was associated with higher overall resistance rates (including co- and cross-resistance). There is plenty of observational research which supports the notion that piperacillin-tazobactam is a less important driver of antibiotic resistance than broad-spectrum cephalosporins[9]. A rational explanation could lie in the fact that broad-spectrum cephalosporins are less effective than inhibitor-based beta-lactams in vitro against ESBLs, which are among the most widespread multidrug-resistant strains within nosocomial environments and could theoretically be preferentially selected under the pressure of inappropriate antibiotic treatment.

On the other hand, Van Loon et al concluded that the homogeneous use of cefpirome, another fourth-generation cephalosporin, was not associated with an increase in the incidence of cefpirome-resistant strains, while both piperacillin-tazobactam and levofloxacin use provoked resistance. The results of those studies are seemingly contradictory and could be confounded by seasonality or breaks in infection control, among other possibilities. Such

discrepancies underline the importance of the use of contemporaneous controls as well as the need for bacterial typing data in future research to facilitate a more meaningful interpretation of the data. Bacterial typing becomes especially important in view of the fact that most studies to date have used the unit-wide incidence of resistant strains as the primary outcome indicator, but this is easily affected by changes in colonization pressure and/or breaks in infection control. An idea for future research would also be to differentiate colonization rates in patient groups within the same ward who have and have not participated in study protocols and use additional wards with similar baseline characteristics as comparison units.

Lack of standardization of research protocols was a crucial issue which limited our ability to evaluate with confidence the replicability of findings and reach safer conclusions. Research protocols differed in terms of the cycle length, the choice of empirical agents, the opportunity to de-escalate, the choice of unit-wide or patient-specific infection or colonization rates as primary endpoints, the acquisition of typing data to assess cross-transmission dynamics, and the measurement of indicators of potential collateral damage induced by the established policies. Among the studies of our dataset it was only Van Duijn et al in 2018 who utilised a cluster-randomised cross-over design to compare cycling with mixing, which was a stronger study design than most. A more thorough evaluation would be possible only if the study included control groups as well as bacterial typing to assess bacterial clonality. It is true that the conduct of research well-designed and rigorous to be of practical use to clinicians requires specialist expertise of multiple kinds, and is logistically difficult. Nevertheless, it is a worthwhile investment which should be co-ordinated by national or international public health agencies with the ultimate aim to safeguard the future value of antimicrobial agents.

Conclusion

Although we cannot exclude the possibility that yet unexplored cycling protocols could show benefits in the future, we believe that the routine use of the currently tested options in clinical practice should not be expected to improve bacterial resistance rates to any appreciable extent. We hope that this review will inspire a more standardised and rigorous approach in the future, as with some upgrading, this type of research could create an enormous contribution to the control of pathogenic bacteria worldwide.

In general, we believe that the usefulness of future research in this area would benefit if researchers utilised the robust cluster randomised design, with randomization at institutional level to reduce contamination, and if they standardised the selection of antibiotic protocols in both baseline/control and cycling arms. This would require substantial background research and profound knowledge of the individual antibiotic agents' mechanisms of resistance induction, as well as organization above the level of an individual hospital. The duration of cycles should be selected on the basis of mathematical predictions of maximal efficacy. Attention should be paid to standardise infection control practices and the allowability or not of de-escalation to narrow-spectrum agents in view of bacterial susceptibility results to eliminate most obvious sources of potential confounding. Careful selection of primary endpoints is important as infection and colonization rates will not be necessarily identical. Other important endpoints should be simultaneously monitored, to

avoid overlooking important ill-effects of the intervention, for example higher levels of clinical error, or a poorer cure to side-effect ratio. Finally, the use of contemporaneous controls within the same unit, the use of other settings with similar baseline characteristics as comparison units, along with bacterial typing would facilitate the investigation of causal associations and the subsequent induction of more meaningful and generalisable conclusions.

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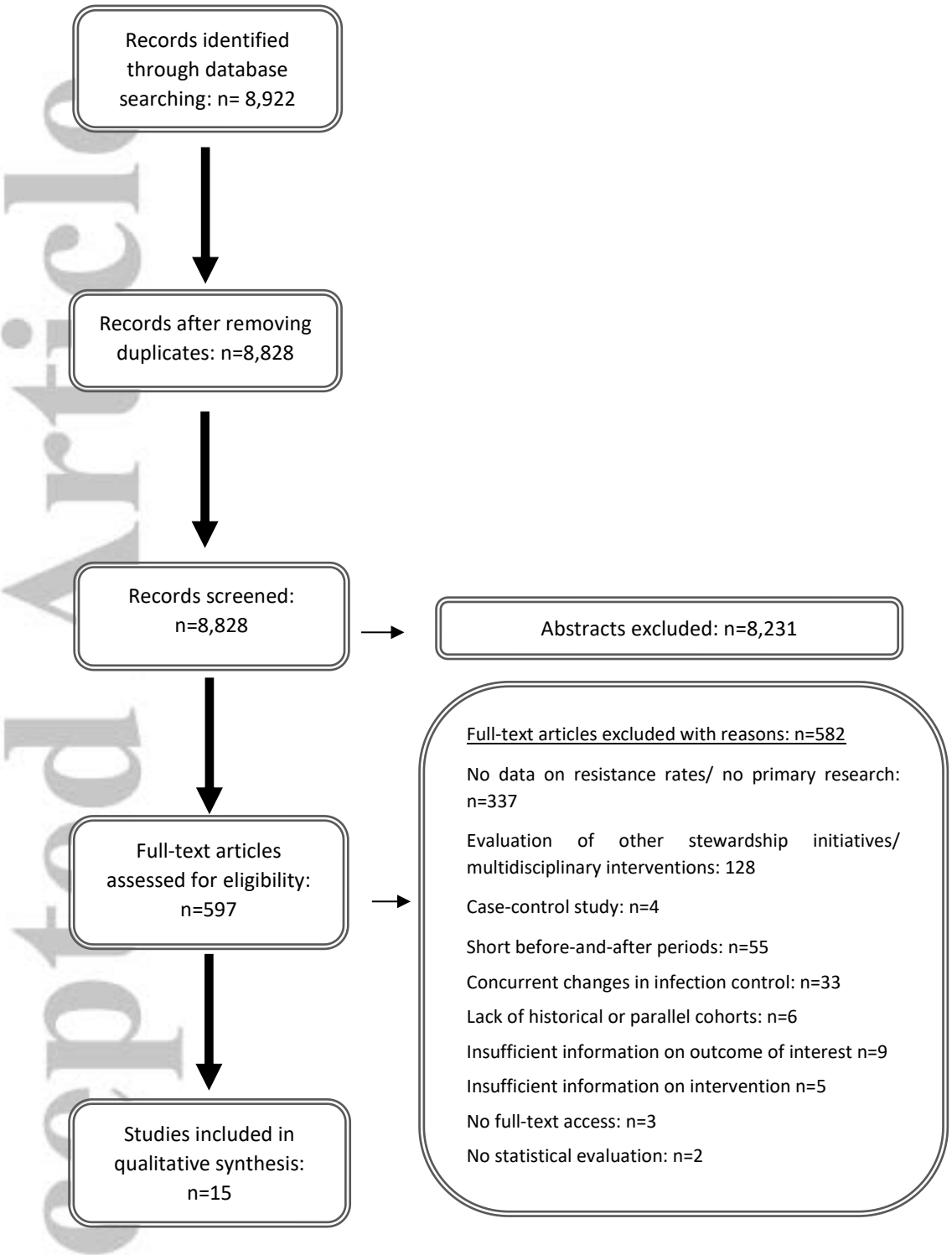

Figure 1: PRISMA chart depicting the study selection process

Table 1: Catalogue of the studies assessing the effects of antimicrobial cycling on bacterial resistance rates; A p value<0.05 was regarded as the statistical threshold of significance and is accordingly recorded as such.

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Toltzis P et al 2002	Controlled trial	Neonatal ICU	Monthly cycling of gentamicin, piperacillin-tazobactam and ceftazidime for suspected infections due to Gram-negative pathogens versus standard practice in the control group (usually ampicillin and gentamicin for suspected infection at birth, vancomycin and gentamicin for hospital-acquired infection, ampicillin and cefotaxime for meningitis, and piperacillin-tazobactam for necrotizing enterocolitis) No de-escalation Typing of bacterial isolates to assess clonality	**PRIMARY** Similar incidence of colonization with resistant bacilli to any antibiotic (10.7% in rotation team versus 7.7% in control team, p=0.09) Similar incidence of colonization with resistant bacilli to the rotated antibiotics (even when only data regarding clonally discordant isolates were considered) (p=0.43 for gentamicin, p=0.08 for piperacillin-tazobactam, p=0.09 for ceftazidime) **OTHER** On-cycle antibiotic use 84.3% for the rotation team Predominant use of gentamicin in the control team (150-250 total antibiotic-days for gentamicin versus <50 total antibiotic-days for piperacillin-tazobactam and ceftazidime) Similar overall antibiotic use (5.31 antibiotic-days for the control team versus 5.67 antibiotic-days for the rotation team, p=0.09) Similar length of stay (12 days for the rotation team versus 10.6 days for the control team p>0.05)	Unit-wide surveillance cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Cadena J et al 2007	Before-and-after	Haematology-Oncology Unit	Cycling of piperacillin-tazobactam and cefepime for the empirical therapy of neutropenic fever every three months versus standard practice during a baseline period (not further clarified) Potential of de-escalation not clarified No typing of bacterial isolates to assess clonality	**PRIMARY** Inconclusive changes in relevant susceptibilities of Enterobacterales and *P. aeruginosa* (p>0.05) Decrease in ampicillin- and vancomycin-susceptible *Enterococcus* spp, (p=0.02 and p=0.001 respectively), decrease in erythromycin- and clindamycin-susceptible *S. aureus* (OR:0.44 95% CI: 0.21-0.90 and OR: 0.14 95% CI: 0.05-0.38 respectively) **OTHER** Increase in cefepime and piperacillin-tazobactam consumption index from 0.003 to 0.88 Increase in cefepime use (p<0.0001)	Unit-wide clinically indicated cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Bennett KM et al 2007	Before-and-after	Surgical ICU	Cycling of piperacillin-tazobactam, imipenem, ceftazidime and ciprofloxacin every month for the empirical treatment of suspected Gram-negative infections (Ciprofloxacin discarded later) versus standard practice during a baseline period (not further clarified) De-escalation permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Increase in piperacillin-tazobactam and ceftazidime-susceptible *P. aeruginosa* proportions (p=0.043 and p=0.002 respectively); No changes for the Medical ICU (Used as a comparison unit.) Inconclusive changes for *E. coli* and *K. pneumoniae* in the Surgical ICU (p>0.4); Increase in piperacillin-tazobactam-resistant *E. coli* proportions (p=0.047) and inconclusive changes for *K. pneumoniae* (p>0.4) in the Medical ICU **OTHER** No information provided regarding secondary outcomes	Unit-wide clinically indicated cultures
Smith R et al 2008	Before-and-after	Surgical ICU	Cycling of vancomycin and linezolid for suspected Gram-positive infections every three months versus primary vancomycin use during a baseline period De-escalation permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Decrease in MRSA incidence rates during cycling (p=0.002) Similar VRE incidence rates (p>0.2) **OTHER** Similar percentage of in-hospital deaths according to initial empirical therapy (p>0.05) Similar incidence rates of *C. difficile* colitis (0.72/100 admissions pre-intervention versus 0.49/100 admissions post-intervention, p>0.05)	Unit-wide clinically indicated cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Nijssen S et al 2009	Prospective comparative cross-over trial	2 ICUs (Medical ICU and Neurosurgery ICU)	Weekly cycling of ceftriaxone, amoxicillin-clavulanate and levofloxacin or ciprofloxacin as empirical treatment versus the homogeneous administration of ciprofloxacin or levofloxacin No de-escalation Typing of isolates to exclude clonal outbreaks	**PRIMARY** Higher colonization rates for ciprofloxacin-resistant isolates (including ciprofloxacin-resistant cephalosporin-resistant isolates) during the homogeneous period ($p<0.01$) Similar colonization rates for cephalosporin-resistant Enterobacteriaceae (14.1/1000 patient-days at risk versus 18.1 patient-days at risk, $p>0.05$) **OTHER** Similar overall antibiotic use ($p>0.05$) Higher ciprofloxacin use during the homogeneous period ($p<0.05$) Lower third-generation cephalosporin use during the homogeneous period ($p<0.05$)	Unit-wide surveillance cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Raineri E et al 2010	Before-and-after	2 ICUs	Cycling of piperacillin-tazobactam, fluoroquinolones, carbapenems, cefepime/ceftazidime every three months for the empirical treatment of VAP versus standard practice in a baseline period (most commonly piperacillin-tazobactam or levofloxacin) No de-escalation No typing of bacterial isolates to assess clonality	**PRIMARY** Similar incidence of VAP due to antibiotic-resistant bacteria (p=0.21) Decrease in cefepime-resistant *P. aeruginosa* isolates (p=0.05) Decrease in cefazolin-resistant *K. pneumoniae* and *E. coli* isolates (p=0.004) No other conclusive changes **OTHER** On-cycle antibiotic use 83% in Unit 1 and 88% in Unit 2 Increase in carbapenem and extended-spectrum penicillin use (p<0.0001) Decrease in aminoglycoside, fluoroquinolone, 3GC and 4GC use (p<0.01) Similar mortality rates (p=0.48)	Respiratory cultures derived from VAP cases

Cumpston A et al 2012	Before-and-after	Blood and Marrow Transplantation Unit	Pre-cycling period: No prophylaxis for neutropenia;* Piperacillin-tazobactam for the empirical treatment of febrile neutropenia Period A: Cycling of imipenem, cefepime plus tobramycin and piperacillin-tazobactam plus tobramycin every eight months for the empirical treatment of febrile neutropenia; Levofloxacin as prophylaxis for neutropenia* Period B: Cycling of agents every three months; Addition of tobramycin in the imipenem arm; Levofloxacin as prophylaxis for neutropenia* *Addition of vancomycin at the discretion of the clinician De-escalation permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Increase in quinolone-resistant Enterobacterales incidence rates (0.1 versus 0.5 versus 1.1 resistant organisms/1000 patient-days respectively, p=0.033) Increase in VRE incidence rates (p=0.005) No other conclusive changes in resistance patterns (p>0.05) **OTHER** Decrease in vancomycin use (397 versus 287 versus 225 DDDs/1000 patient-days respectively) Similar use of cefepime, piperacillin-tazobactam and imipenem across the four most recent years of cycling (p=0.12) Decrease in the incidence rate of *Klebsiella spp* and *E. coli* bacteremia (p<0.0001 and p=0.003 respectively) and candidemia (p=0.022) Similar morbidity and mortality incidence rates (p=0.713)	Unit-wide blood cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Chong Y et al 2013	Before-and-after	Haematology Unit	Monthly cycling of piperacillin-tazobactam, ciprofloxacin, meropenem and cefepime for the empirical treatment of neutropenic fever versus the homogeneous use of cefepime during a baseline period Potential of de-escalation not clarified No typing of bacterial isolates to assess clonality	**PRIMARY** Blood isolates: Decrease in cefepime-resistant isolate incidence from 6/13 (70% of those were ESBLs) to 01/14 (p=0.007); Decrease in ciprofloxacin-resistant isolate incidence (p=0.048) Stool isolates: Decrease in ESBL and ciprofloxacin-resistant *E. coli* incidence (p<0.001) **OTHER** Similar mortality rates (p=1.0) 65.9% decrease in unit-wide cefepime use	Blood and stool cultures from patients with neutropenic fever
Teranishi H et al 2017	Before-and-after	Paediatric Haematology Unit	Monthly cycling of piperacillin-tazobactam, meropenem and cefepime versus the homogeneous prescription of cefpirome as empirical treatment for neutropenic fever during a baseline period No de-escalation No typing of bacterial isolates to assess clonality	**PRIMARY** Blood isolates: Decrease in ESBL incidence from 5/15 to 0/15 isolates (p< 0.05) Nasal and stool isolates: Decrease in ESBL incidence from 15/33 to 0/33 isolates (p<0.01) Similar MRSA and VRE incidence in blood, stool and nasal cultures (p>0.05) **OTHER** No information provided regarding secondary outcomes	Blood, nasal and stool cultures from patients with neutropenic fever

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Tsukayama D et al 2004	Comparative trial	ICU	Cycling of ciprofloxacin or levofloxacin plus clindamycin or metronidazole and piperacillin-tazobactam every four months as first-line empirical treatment De-escalation permitted Typing to assess clonality of bacterial isolates	**PRIMARY** No correlation between particular antibiotic class consumption and onset of resistance (p>0.05) **OTHER** Off-cycle antibiotic use not drastically reduced	Unit-wide surveillance units
Van Loon H et al 2005	Comparative trial	ICU	Cycling of levofloxacin plus aminoglycoside and beta-lactam plus aminoglycoside (cefpirome in one cycle and piperacillin-tazobactam in the other) every four months for suspected Gram-negative infections No de-escalation No typing of bacterial isolates to assess clonality	**PRIMARY** Colonization rates for Gram-negative bacteria resistant to levofloxacin higher in periods of exposure (p=0.003) Colonization rates for Gram-negative bacteria resistant to cefpirome similar between periods of exposure and non-exposure (p=0.85) Colonization rates for Gram-negative bacteria resistant to piperacillin-tazobactam higher in periods of exposure (p=0.02) **OTHER** On-cycle antibiotic use 88.5%-100%	Unit-wide surveillance cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Ginn A et al 2012	Comparative trial	2 ICUs	Cycling of piperacillin-tazobactam and cefepime for the empirical therapy of sepsis every four months Potential of de-escalation not clarified Typing of isolates to exclude clonal outbreaks	**PRIMARY** Proportion of admissions complicated by antibiotic-resistant isolates higher in cefepime cycles (p<0.001) Proportion of admissions complicated by MRSA higher in cefepime cycles (p=0.01) **OTHER** Similar risk of admissions complicated by any infection (p>0.05) On-cycle antibiotic use>60% of total use Off-cycle antibiotic use<15% of total use	Unit-wide clinically indicated cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Martinez J et al 2006	Comparative cross-over trial	2 ICUs	1st arm: Cycling of cefepime (or ceftazidime), ciprofloxacin, carbapenems, and piperacillin-tazobactam every month for suspected *Pseudomonas* infections 2ndarm: Successive administration of these agents to consecutive patients Potential of de-escalation not clarified Combination therapy permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Higher proportion of patients colonised with cefepime-resistant *P. aeruginosa* during mixing (p=0.01) Inconclusively higher proportion of ceftazidime and carbapenem-resistant *P. aeruginosa* during mixing (p=.0.06 and 0.07 respectively) No other significant differences with regard to other Gram-negatives species (p>0.05) **OTHER** Higher mortality rates during cycling mainly attributable to Unit 2 (p=0.01) Higher use of carbapenems and piperacillin-tazobactam (p=0.004 and p=0.04 respectively) and lower use of cephalosporins during mixing (p<0.0001)	Unit-wide surveillance cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Van Duijn PJ et al 2018	Cluster randomised cross-over trial	Multi-centre ICU	Cycling of 3GC (or 4GC), carbapenems and piperacillin-tazobactam every six weeks versus mixing those agents (administering those successively to consecutive patients) for empirical treatment of suspected Gram-negative infections De-escalation permitted Combination therapy permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Similar prevalence of antibiotic-resistant Gram-negative bacteria (p=0.64) Similar incidence rate ratio of antibiotic-resistant Gram-negative bacteria adjusted for hand hygiene compliance, patient-sex and proportion of short-stay patients (p=0.73) Similar prevalence of ESBLs (p>0.2), and carbapenem-resistant non-fermenters (p>0.6); Higher prevalence of piperacillin-tazobactam-resistant *P. aeruginosa* isolates during cycling (5% versus 3%, p=0.04) and similar prevalence of piperacillin-tazobactam-resistant *A. baumannii* isolates (p>.0.6) **OTHER** Similar mortality rates and similar length of stay during periods of mixing and cycling (p=0.38) Similar overall use of antibiotics (p=0.93) and similar use of study antibiotics between study periods ((p: 0.08-0.8 depending on antibiotic class) Three times higher use of on-cycle antibiotics compared to off-cycle use	Unit-wide surveillance cultures

Authors	Study Design	Setting	Protocol	Outcomes	Indicator
Jayashree M et al 2020	Comparative trial	Paediatric ICU	Period 1: Mixing piperacillin-tazobactam, imipenem and cefepime (administering those successively to consecutive patients) for suspected Gram-negative infections Period 2: Cycling the aforementioned agents every month De-escalation permitted Combination therapy permitted No typing of bacterial isolates to assess clonality	**PRIMARY** Higher percentage of resistant isolates during the baseline period than in mixing, cycling and washout periods (p<0.001) Similar percentage of resistant isolates during mixing and cycling (p=0.29) **OTHER** Similar mortality rates between periods (p=0.72) Similar episodes of healthcare-associated infections during mixing and cycling but lower than baseline (p=0.34 and p<0.001 respectively) Similar overall use of antibiotics between all phases (p=0.34)	Unit-wide surveillance cultures

List of abbreviations: ICU: Intensive Care Unit, MRSA: Methicillin-resistant *Staphylococcus aureus*, VAP: Ventilator-associated Pneumonia, VRE: Vancomycin-resistant *Enterococcus*, ESBL: Extended-Spectrum Beta-Lactamase, 3GC: 3rd Generation Cephalosporin, 4GC: 4th Generation Cephalosporin