The potential for developing new antimicrobial resistance from the use of medical devices containing chlorhexidine, minocycline, rifampicin and their combinations: a systematic review

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Background: Catheter infections remain one of the most persistent adverse events causing significant morbidity, economic impact and mortality. Several strategies have been proposed to reduce these infections including the use of catheters embedded with antibiotics and/or antiseptics. One reoccurring challenge is the fear that antimicrobial medical devices will induce resistance. The aim of this systematic review is to evaluate the evidence for induced antimicrobial resistance caused by exposure to antimicrobial medical devices.

Methods: Four electronic databases [MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Scopus] were screened for studies published between 1983 and 2019 regarding assessment of microbial resistance with use of medical devices containing chlorhexidine, minocycline, rifampicin or combinations thereof. Development of new resistance, selection for tolerant organisms and ‘no change in resistance’ were assessed.

Results: Forty-four publications, grouped by study type and stratified by drug assessed, were included for analyses. The majority of studies found no change in resistance after exposure to antimicrobial medical devices (13 in vitro, 2 in vivo, 20 clinical). Development of new resistance was commonly reported with the use of rifampicin as a single agent and only reported in one study assessing the minocycline/rifampicin combination (M/R); however, the increase in MIC was well below clinical relevance.

Conclusions: Emergence of new resistance to combinations of M/R, minocycline/rifampicin/chlorhexidine (M/R/CH) and chlorhexidine/silver sulfadiazine (CHXSS) was rare. No clinical trials confirmed its occurrence and some refuted it. The risk of development of new resistance to these antimicrobial combinations appears more fear-based than substantiated by clinical and experimental evidence but warrants continued surveillance.

Introduction

Central line-associated bloodstream infections (CLABSI) remain one of the most persistent post-insertion adverse events causing significant morbidity as well as substantial economic impact and mortality.1 Central lines coated with antimicrobial agents were introduced to reduce the risk of CLABSI.2 While using antimicrobial catheters can potentially reduce the risk of CLABSI, their use introduces other risks to patients.3,4 These include irritation and inflammatory responses to the antimicrobial agents, allergic reactions to the antimicrobial agents, breakthrough infections by virulent organisms against which the antimicrobial agents have limited effectiveness and the induction of antimicrobial resistance through prolonged exposure to the antimicrobial agents on the catheters. Allergic reactions by patients to the agents in the antimicrobial central lines (most commonly chlorhexidine) have been rare and doses of antimicrobial agents on catheters have been titrated to levels generally producing acceptably biocompatible responses following contact with the antimicrobial agents on the devices.5 Antimicrobial resistance is the result of organisms defensively adapting to exposure to subinhibitory or sublethal doses of antimicrobial agents and developing defensive mechanisms whereby the microbes are able to thwart and render ineffective the mechanisms of action of the antimicrobial agents.6 The consequence of antimicrobial resistance is that microbes may become more virulent and, when they cause infections, there may be fewer...
and potentially more toxic antimicrobial drugs that are available to treat the infections.

Two antimicrobial catheter treatments that are combinations of different agents have been widely studied and have been recommended by the CDC at the level of category 1A. One is a triple combination of two antiseptic agents and one antibiotic, specifically chlorhexidine/silver sulfadiazine (CHXSS), and the other is a combination of two antibiotics, specifically minocycline and rifampicin (M/R). Studies on the first-generation CHXSS catheter, performed at a time before rigorous hygienic insertion practices were widely adopted, demonstrated significant reduction in CLABSIs. Subsequent large prospective randomized clinical trials (RCTs) conducted following the adoption of modern insertion practices with a second-generation CHXSS catheter, having significantly higher chlorhexidine content, have repeatedly failed to significantly reduce CLABSIs. A peripherally inserted central catheter (PICC) containing chlorhexidine as a sole antimicrobial agent similarly failed to reduce CLABSIs in a randomized prospective trial when compared with a non-antimicrobial PICC. Several meta-analyses have reinforced the ineffectiveness of CHXSS catheters in preventing CLABSIs. Nevertheless, chlorhexidine-based catheters remain widely used. In contrast, the M/R catheter has significantly reduced CLABSIs in multiple randomized prospective clinical trials and several meta-analyses have further reinforced the effectiveness of the M/R combination in reducing CLABSIs. The enhanced antimicrobial activity from combining chlorhexidine with M/R on catheters has been reported and the combination proposed for future use. We therefore focus in this systematic review on the evidence for induced antimicrobial resistance caused by exposure to catheters and other medical devices containing chlorhexidine, minocycline, rifampicin and combinations thereof because of the prevalence of their use and extensive history of published in vivo, in vivo and clinical studies.

Methods
Search strategy
Four electronic databases [MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Scopus] were searched for studies assessing resistance to rifampicin, minocycline or chlorhexidine that were published between 1983 and February 2019. Search terms were mapped to the MeSH headings (MEDLINE) and Emtree terms (Embase). The following search string was used: (rifampin OR rifampicin OR minocycline OR chlorhexidine) AND (central venous catheter OR catheters OR catheter, indwelling OR vascular access devices OR catheterization, central venous OR CVC OR catheterization, peripheral OR PICC OR bandages OR bandages, hydrocolloid OR biological dressings OR occlusive dressings OR prophylaxis and implants OR dental implants OR penile prosthesis OR pacemaker, artificial OR pacemaker OR catheter dressing OR dressing OR penile implant OR disinfection OR wipes) AND (drug resistance OR drug resistance, microbial OR drug resistance, bacterial OR drug resistance, fungal OR resistance OR antibiotic resistance OR emerging antibiotic resistance).

Search results were first screened by title and abstract by two independent reviewers. Any disagreements were discussed by authors to an agreed-upon consensus. Resulting articles were read for full-text review and data abstraction. Relevant references cited in primary literature were also screened to be included in analyses. Manuscripts were excluded if they were in a language other than English, were conference abstracts, did not assess the drug combination of interest (minocycline, rifampicin, chlorhexidine or combination thereof), did not assess a medical device (i.e. systemic use of drug agents), did not directly assess development of resistance or were a descriptive case series. Literature reviews were also excluded from the primary assessment and will be summarized independently.

Data abstraction
All primary literature to be abstracted were first classified into in vitro, in vivo or clinical study types. Manuscripts with more than one study type had data extracted from each type. All data abstracted from each manuscript were recorded electronically in the data abstraction form (DAF). Data from the DAF were then organized by spreadsheet for assessment. Quality control was assessed periodically to ensure accurate transfer of abstracted data. Data, including (i) study objective; (ii) device assessed; (iii) drug assessed; (iv) method for drug attachment to device; (v) method for assessing resistance; (vi) results; and (vii) conclusions were collected from each study type. Data from in vitro studies also included organisms assessed (challenge organisms) and their antimicrobial resistance profiles. Data abstraction pertaining to in vivo animal models included species and number of animals tested as well as organisms assessed (challenge organisms) and their antimicrobial resistance profiles. Clinical studies included data abstraction for study design (retrospective, prospective, case–control or RCT) and objective, number of patients assessed, causative organisms being treated with the antimicrobial device and their resistance profiles.

Definitions
Based on authors’ conclusions regarding the potential for developing resistance after exposure to antimicrobial devices, each manuscript was categorized as follows:

1. No change in (antimicrobial) resistance
2. Selection for (antimicrobial agent-) tolerant strains (clinical studies only)
3. Development of new (antimicrobial) resistance
4. (Antimicrobial) resistance not assessed

‘No change in antimicrobial resistance’ was defined as no or inconsequential shift in MIC after use of antimicrobial devices. ‘Selection for antimicrobial agent-tolerant strains’ was defined as an increasing shift in MIC for the single agent or combination of agents; however, MIC remained below the threshold for clinical susceptibility (i.e. below CLSI cut-offs for resistance). ‘Development of new antimicrobial resistance’ was defined as a clinically consequential shift in MIC to concentrations above the CLSI resistance concentration cut-off for clinical susceptibility.

Quality assessment
To assess quality and bias in each manuscript, any critique to study design, methodology or conclusions based on presented data was also recorded in the DAF. Clinical studies were assessed for bias using the National Heart, Lung, and Blood Institute Study Quality Assessment Tools (2018). Clinical studies were stratified by study type (observational, case–control and controlled intervention trial) and then scored based on the questions examining various reporting measures. Observational studies were scored out of 12 points and had questions focused on study objective, population, exposures of interest and validated measurements of outcome. Case–control studies were scored out of 13 points and had questions focused on study objective, population, selection of cases and controls, exposures of interest and validated measurements of outcome. Clinical intervention trials were scored out of 14 points and had questions focused on study objective, randomization, blinding, interventions and adherence to intervention protocols, sample size and validated measurements of outcome.

For in vivo and in vivo studies, articles were assessed for bias using the Animal Research: Reporting in vivo experiments (ARRIVE) guidelines. While the ARRIVE guidelines were originally developed for in vivo studies,
they have been adapted and assessed for quality criteria in in vitro studies. In vitro studies were scored out of 19 and had questions pertaining to reporting of study objective and design, experimental procedure, use of appropriate controls, validated measurements of outcome and analyses. In vivo studies were scored out of 23 and had questions pertaining to reporting of study objective and design, experimental procedure, animal husbandry, exposures and controls, blinding, validated measurements of outcome and analyses.

Finally, all studies were graded with a score of A–D on methodology used for assessment of examining development of resistance. Articles were scored as follows:

1. Grade A if the article described AND referenced a validated model for assessing resistance such as CLSI or EUCAST methods for MIC or MBC.
2. Grade B if the article either described OR referenced a validated model for assessing resistance.
3. Grade C if the article assessed resistance with a method other than a microbiologically validated model (i.e. presence of resistance genes) or resistance was assessed only from the hospital record.
4. Grade D if the article did not describe or reference any method for resistance (i.e. only stated that resistance was assessed).

**Results**

**Search strategy**

Searches in MEDLINE, Embase, CINAHL and Scopus identified 526, 1040, 85 and 421 studies, respectively, for a total 2072 citations. Title and abstract screening identified 183 studies, 66 of which were duplicates, resulting in a total of 127 studies for full-text review. During full-text review, 19 studies were excluded because they did not assess one of the target drugs or drug combination, 13 studies were excluded because no antimicrobial device was assessed, 4 were excluded because they were conference abstracts/proceedings that did not contain complete data for analyses, 4 studies were excluded because they were descriptive case series and 23 were excluded because they didn't directly assess development of resistance. These studies typically reported whether organisms broke through with the use of an antimicrobial device, indicating that the antimicrobial device was not efficacious, not whether organisms developed resistance. Though CHXSS is a drug combination of chlorhexidine and silver sulfadiazine, which is not specifically our drug combination of interest (chlorhexidine, minocycline and rifampicin), it was included for assessing the potential for developing new resistance against chlorhexidine combinations. Additionally, 26 manuscripts were identified as literature reviews and will be summarized independently. An additional six studies were identified by screening bibliographies of primary literature and were included in analyses. A total of 44 publications were included for qualitative assessment of the potential for developing new resistance after being exposed to antimicrobial medical devices (Figure 1).

**Study characteristics**

Characteristics and results of all in vitro studies included are summarized in Table 1, in vivo studies in Table 2 and clinical studies in Table 3.

**In vitro**

A total of 18 in vitro studies were included in the analyses (Table 1), including 4 studies assessing rifampicin alone,18–21 9 studies assessing chlorhexidine (CH or CHXSS),22–30 2 studies assessing M/R31,32 and 1 study assessing the triple combination of M/R/CH.33 Two studies assessed multiple drugs: Sampath et al.34 assessed the CHXSS and M/R combinations and Tambe et al.35 assessed minocycline, rifampicin, M/R and CHXSS. Three different devices (wipes/scrub,23–30 vascular grafts18,19,21 and catheters20,22,31–35) were assessed. Figure 2a depicts the device and drug combinations.

Authors reported no change in resistance in eight studies assessing exposure to devices containing chlorhexidine,22–27,29,30,34 two studies assessing M/R,31,32 one study that assessed minocycline alone35 and the one study that assessed M/R/CH.33 Development of new resistance was reported in five studies, the majority of which assessed rifampicin alone.18–21,35 Two studies concluded that resistance developed after exposure to M/R34,35 and one with exposure to chlorhexidine.28

**In vivo**

Three in vivo studies were included in the analyses (Table 2), all of which assessed rifampicin alone18,36,37 in vascular graft models. Two studies assessed rifampicin-soaked vascular grafts in a sheep model16,37 and one study assessed colonized vascular grafts with aqueous rifampicin in a subcutaneous mouse model.18 Figure 2a depicts the device and drug combinations studied.

Most in vivo studies with full-text review assessed efficacy of the antimicrobial device (breakthrough) and did not assess...
| Citation                  | Drug | Device                  | Concentration(s) | Organisms assessed | Methodology; resistance measurement | Results                                                                 |
|--------------------------|------|-------------------------|------------------|--------------------|--------------------------------------|-------------------------------------------------------------------------|
| Bayston et al., 2009     | R    | peritoneal catheter     | 0.2%             | SE                 | Growth within ZOI during serial plate | MIC of SE increased from 0.008 to >32 mg/L after 9 days exposure to 0.2% R |
|                          |      |                         |                  |                    | transfer; MIC Etest                   | development of new resistance                                          |
| Berard et al., 2019      | R    | vascular graft          | 5000 mg/L        | SE, MRSA, EC, CA   | MIC of SE and SA increased to         | development of new resistance                                          |
|                          |      |                         |                  |                    | >512 mg/L after 7 days exposure to R  |                                                                          |
|                          |      |                         |                  |                    | mutations of rpoB gene confirmed by   |                                                                          |
|                          |      |                         |                  |                    | sequencing                            |                                                                          |
| Bergamini et al., 1996   | R    | vascular graft          | 4×, 64×, 100×,   | SE colonized on     | R decreased biofilm concentration     | development of new resistance                                          |
|                          |      |                         | 1000× MIC        | vascular graft     | at 4 h but was ineffective at 18 and 42 h due to MIC increasing from 0.1 to >30 mg/L R |                                                                          |
| Garrison et al., 1997    | R    | uncoated vascular graft | aqueous R at     | SE                 | Biofilm eradication; R MIC by disc    | development of new resistance                                          |
|                          |      |                         | 4×, 1000× MIC    |                    | diffusion                            |                                                                          |
| Aarestrup et al., 2004   | CH   | environmental           | —                | Salmonella (156),  | MIC of all recovered SE increased     | no change in resistance                                                 |
|                          |      | (used for disinfection  |                  | EC (202), SA (43), | from baseline (0.1 mg/L) to >30 mg/L |                                                                          |
|                          |      | in food animals)        |                  | Staphylococcus     |                                                                          |                                                                          |
|                          |      |                         |                  | hyicus (38),       |                                                                          |                                                                          |
|                          |      |                         |                  | Enterococcus      |                                                                          |                                                                          |
|                          |      |                         |                  | faecalis (52),     |                                                                          |                                                                          |
|                          |      |                         |                  | Enterococcus      |                                                                          |                                                                          |
|                          |      |                         |                  | faecium (78)       |                                                                          |                                                                          |
| Apisarnthanarak et al.,  | CH   | CH wipes                | —                | AN (100); pre-CH  | MIC microbrath dilution             | no change in resistance                                                 |
| 2014                     |      |                         |                  | (50), post-CH (50) |                                                                          |                                                                          |
| Ekizoglu et al., 2016    | CH   | —                       | MIC 0.125–512 mg/L; eradication 0.02%–4% | PS (22); AN (19); SM (13); KB (14); EB (15); MSSA (6); MRSA (15); EN (17) | MIC agar dilution, planktonic eradication; not conducted | no change in resistance (per Discussion section)                         |
|                          |      |                         |                  |                    |                                                                          |                                                                          |
| Johnson et al., 2013     | CH   | —                       | —                | MRSA: qacA/B+ (5), smr + (5), no plasmid (5) | CBC                                | no change in resistance                                                 |

**Table 1. In vitro assessment of potential resistance to rifampicin, minocycline and/or chlorhexidine**
| Study | CH | Hand scrub | Resistance test method | MIC/MBC result | CH susceptibility changes |
|-------|----|------------|------------------------|----------------|--------------------------|
| Martro et al., 2003 | CH | Hibiscrub | PRI, D, A | Eradicated all AN strains tested | No change in resistance |
| Modak et al., 1992 | CH | CHXSS | PRI | MIC after 25 serial subinhibitory passages | 2-Fold increase in MIC for SA and EC tested against CH, SS and CHXSS |
| Skovgaard et al., 2013 | CH | CH hand scrub | PRI | MIC/MBC by disc diffusion | No difference in CH susceptibility in hospital versus community versus historic; no selection for qacA/B genes in hospital versus community versus historic (no genes present) |
| Suwantarat et al., 2014 | CH | CH cloths for skin antisepsis | PRI | MIC/MBC by microbroth dilution | Patients with daily CH bathing were more likely to have an organism with reduced CH susceptibility (86% versus 64% P = 0.028) |
| Wesgate et al., 2016 | CH | — | PRI | MIC measures of short and long exposure | No change in the CH susceptibility profile after short and long exposures to the CH |
| Munson et al., 2004 | M/R (n = 2) | Spectrum CVC (Cook Critical Care) | PRI | Organisms cultured from border of ZOI from M/R catheter; MIC disc diffusion | Colonies sampled from growth around ZOI failed to demonstrate emergence of resistance to M or R by disc diffusion |
| Norton et al., 2001 | M/R | Umbilical catheters | PRI | ZOI, biofilm colonization; disc diffusion | ZOI showed efficacy to all organisms tested except PS and CA; CoNS and SM in the study remained sensitive to M and R |
| M/R/CH (n = 1) Rosenblatt et al., 2019 | M/R/CH | CVC | PRI | 20 serial passages through subinhibitory concentration; MIC microbroth dilution | All except one organism remained within 2-fold change in MIC after 20 passages; one strain of EB showed a 4-fold increase in MIC after 20 passages but after passages in broth (no M/R/CH) the MIC returned within the 2-fold limit |

Multiple drug combinations (n = 2)
Table 1. Continued

| Citation         | Drug  | Device      | Concentration(s) | Organisms assessed | Methodology: resistance measurement | Results                                      |
|------------------|-------|-------------|------------------|--------------------|-------------------------------------|---------------------------------------------|
| Sampath et al.,  | CHXSS | CVC, CHXSS  | —                | SE, EC             | 20 serial passages through subinhibitory concentration; MIC tube dilution | CHXSS: no change in resistance; M/R: development of new resistance |
| 2001             | M/R   | (Arrowguard Plus, M/R (Spectrum) | —                | SE                               | M: NS increase in MIC; R: 25 000-fold increase in MIC; M/R: 10-fold increase for ATCC strain, 16-fold increase for clinical strain; CHXSS: NS increase in MIC |
| Tambe et al.,    | M, R  | M/R, CHXSS  | —                | SE                 | 20 serial passages through subinhibitory concentration; MIC tube dilution | CHXSS: no change in resistance; M/R: development of new resistance |
| 2001             |       | CHXSS       | —                |                    |                                     |                                             |

M, minocycline; R, rifampicin; CH, chlorhexidine; SS, silver sulfadiazine; ZOI, zone of inhibition; NS, not significant; MRSE, methicillin-resistant SE; EN, Enterococcus species; AN, Acinetobacter species; KB, Klebsiella pneumoniae; PS, Pseudomonas aeruginosa; SM, Stenotrophomonas maltophilia; EB, Enterobacter species; CB, Citrobacter species; CA, Candida albicans; CP, Candida parapsilosis G+, Gram-positive organisms; G−, Gram-negative organisms; —, data not presented in the manuscript being abstracted.

Quality assessment

Of the literature reviews assessed, the majority discussed literature pertaining to other primary endpoints such as bloodstream infection. Of the abstracts assessed, antimicrobial exposure, efficacy of antibiotics/biocides in infection control, and de novo resistance after contact with the device, which of the following does the study show: (i) no change in resistance; or (ii) development of new resistance.

24 (12.5%) were graded ‘D’. In the assessment of clinical studies, observational studies, scores from 18 to 21 (out of 23) were graded ‘A’, while the majority of studies found no change in resistance after exposure to a rifampicin vascular graft, two of which reported development of new resistance after implanting both M/R-coated and uncoated grafts.

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After contact with the device, which of the following does the study show: (i) no change in resistance; or (ii) development of new resistance.

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Table 2. In vivo assessment of potential resistance to rifampicin, minocycline and/or chlorhexidine

| Citation            | Drug      | Device: how is drug attached; concentration | Animal model species (n); implant site; duration | Organism(s) assessed | Methodology; resistance measurement | Results                                                                 |
|---------------------|-----------|---------------------------------------------|-------------------------------------------------|---------------------|--------------------------------------|------------------------------------------------------------------------|
| Avramovic et al., 1991\(^{16}\) | R         | vascular graft; soaked in 100 mg aqueous R   | sheep (20); carotid artery; 3 weeks              | SA                  | Breakthrough ZOI; R antibiotic disc  | All SA isolated from R-treated grafts remained sensitive                |
| Garrison et al., 1997\(^{18}\) | R         | uncoated vascular graft; aqueous 4\(\times\) and 1000\(\times\) MIC R infused in subcutaneous pocket | mouse (42); subcutaneous pocket; 4, 18 and 42 h | SE                  | Biofilm eradication; MIC broth dilution | MIC of recovered SE from high-dose R increased from BL (0.1 to >30 mg/L) |
| Sardelic et al., 1995\(^{27}\) | R         | vascular graft; soaked in 1.2 mg/mL aqueous R | sheep (9); carotid artery; 3 weeks               | MRSA                | Breakthrough MIC; agar dilution     | Breakthrough MRSA had same R MIC as starting inoculum                 |

ZOI, zone of inhibition; BL, baseline.

Discussion

The focus of this review was evidence in the literature for the development of antimicrobial tolerance versus selection of tolerant strains. For this review, development of new antimicrobial resistance to minocycline, rifampicin and chlorhexidine is taken as a complete loss of inhibitory or bactericidal effect at therapeutically achievable concentrations due to adaptive changes by organisms following exposure to minocycline, rifampicin and/or chlorhexidine. Development of antimicrobial tolerance can be a result of organisms responding to the presence of antimicrobial agents by expressing similar adaptive genes that phenotypically alter the concentrations of antimicrobial agents required to be effective. In some cases there is a limit to the concentration of interfering molecules an organism can express and in others less efficient alternative pathway responses result in incomplete or inefficient inactivation of the effects of the antimicrobial agent. Selection of tolerant strains from developed antimicrobial tolerance responses typically is seen as shifts in MICs of antimicrobial agents to higher MICs in order to be effective. In some cases there is a limit to the concentration of interfering molecules an organism can express and in others less efficient alternative pathway responses result in incomplete or inefficient inactivation of the effects of the antimicrobial agent. Selection of tolerant strains from developed antimicrobial tolerance responses typically is seen as shifts in MICs of antimicrobial agents to higher MICs in order to be effective.

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| Citation                  | Study type (n patients) | Device; drug                          | Design                                                                 | Measure of resistance | Results                                                                 | After contact with the device, which of the following does the study show: (i) no change in resistance; (ii) selection for tolerant strains; or (iii) development of new resistance |
|--------------------------|-------------------------|----------------------------------------|------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| **Rifampicin (n = 1)**   |                         |                                        |                                                                        |                       |                                                                         |                                                                                                                               |
| Bandyk et al., 200140    | retrospective (27)       | vascular graft soaked in aqueous R (45–60 mg/mL) | Patient with graft infections had graft replaced with R-soaked graft | not stated            | Failure from MRSA infection and recurrent R-resistant SE infection in 2 patients; 18 patients remained infection free and survived | selection for tolerant strains; discussion: ‘need for continued evaluation to determine whether R grafts select for resistant G+’ |
| **Chlorhexidine (n = 14)** |                         |                                        |                                                                        |                       |                                                                         |                                                                                                                               |
| Batra et al., 201041     | retrospective (4570: 2480 pre, 2090 post) | CH bathing; Hibitane, 1% CH dusting powder, Hibiscrub | Assessed for MRSA infection pre- and post-antiseptic protocol | MBC (CLSI)            | Decrease in MRSA infections by endemic strain but increase in MRSA infection by outbreak strain after initiation of CH baths; all outbreak strains had qacA/B genes and 3-fold higher MBCs than endemic strain | selection for tolerant strains                                                                                                   |
| Choudhury et al., 201746 | prospective (77: 43, CH dressing, 34 no CH dressing) | CH dressings at catheter insertion sites | Prevalence of smr or qacA/B from DNA from skin with CH dressing versus skin with no (or non-CH) dressing | assessment of smr or qacA/B genes by PCR | No significant difference in frequency of qacA/B and smr recovered from CH dressing versus no CH dressing; no evidence that CH increases frequency of CH-tolerance genes at catheter sites | no change in resistance                                                                                                       |
| Chung et al., 201548     | prospective (3054: 1514 pre, 1540 post) | CH wipes                          | Assessment of AN infections pre- and post-CH bathing | MIC microbroth dilution | Prevalence of AN decreased from 25.8% to 18.2%; no difference in CH MIC between 42 AN in pre-CH bathing and 56 AN in post-CH bathing | no change in resistance                                                                                                       |
| Ho et al., 201248        | case-control (156: 96 MRSA; 60 MSSA) | CHXSS CVC (Arrowguard blue) | Assessment of MIC and qacA/B or smr genes from MRSA and MSSA catheter-related infection | MIC agar dilution; prevalence of genes by PCR | Significantly more MRSA isolates containing qacA/B genes caused CHXSS-impregnated CRBSI; MIC stratified for CHXSS catheter not assessed | selection for more tolerant strains                                                                                               |
| Lee et al., 201149       | case-control (150: 75 case; 75 control) | CH wipes for decolonization | Assessed risk factors for persistence of MRSA carriage after decolonization | presence of resistance genes by PCR | Genotypic CH resistance alone did not predict persistent MRSA carriage | no change in resistance                                                                                                       |
| Study              | Design          | Intervention | Target Organism | Methodology | Findings                                                                 |
|--------------------|-----------------|--------------|-----------------|-------------|--------------------------------------------------------------------------|
| Lowe et al., 2017  | Prospective     | CH wipes     | MRSA and VRE    | MIC agar dilution; presence of resistance genes by PCR | In intervention group, one MRSA and one MSSA contained resistance genes though MIC was susceptible; one MRSA had resistant MIC (8 mg/L) but was not PCR positive |
| Mendoza-Olazaran et al., 2014 | Prospective   | CH wipes     | AN infections   | MIC agar dilution | AN isolates in the CH bathing period showed a significant decrease in CH MIC likely due to change in clonality of infecting isolate |
| Maki et al., 1997  | RCT             | CHXSS CVC    | Susceptibility  | ZOI          | None of isolates from infected catheters showed resistance to fresh CHXSS catheters by ZOI |
| McNeil et al., 2016 | Retrospective  | CH wipes     | Assessed CH MIC, smr and qacA/B over time; increased CH bathing over time | MIC microbroth dilution; prevalence of genes by PCR | Increased prevalence of smr and qacA/B in SA infections over time; however, non-significant difference of CH MIC for isolates positive and negative for genes |
| Schlett et al., 2014 | Cluster RCT     | CH wipes, Hibiclens | MIC, qacA/B from MRSA SSTI among standard bathing versus CH bathing | MIC microbroth dilution; prevalence of genes by PCR | No difference in MIC or prevalence qacA/B in CH bathing versus control |
| Schuerer et al., 2007 | Prospective   | CHXSS CVC    | Assessment of CRBSI in control versus CHXSS | not conducted | No significant difference in rate of CRBSI or microbiological profile organisms cultured in control versus CHXSS |
| Soma et al., 2012  | Prospective     | CH wipes     | MIC, qacA/B among CoNS sampled from patients with no, moderate or heavy CH baths | MIC microbroth dilution; prevalence of genes by PCR | No significant difference in CH MIC in no versus moderate versus heavy CH samples. 11/17 CoNS had qacA/B |
| Timsit et al., 2009 | RCT             | CH-impregnated sponges | Assessment of CRI, and MBC in CH sponge versus control | MBC          | Reduction in CRI with use of CH sponge; no difference in MBC for control versus CH sponge |
| Velazquez-Meza et al., 2017 | Prospective   | CH wipes (2%) | MIC of SA isolates from pre-, during and post-CH bathing | MIC agar dilution | No isolates showed reduced susceptibility to CH in pre-versus during versus post-intervention |

Continued
| Citation                  | Study type (n patients) | Device; drug                          | Measure of resistance  | Results                                                                                                                                                                                                 |
|--------------------------|------------------------|---------------------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chatzinikolaou et al. 2003 | RCT (130: 66 M/R, 64 controls) | M/R CVC, haemodialysis                 | CRBSI; MIC of CoNS cultured from colonized catheters | MIC microbroth dilution of CoNS isolates from colonized catheters were similar in M/R versus control M/R and M/R versus controls. All 67 SA and SE isolates were susceptible to M; one isolate (M/R) and 9 isolates (control) were resistant to R. |
| Chatzinikolaou et al. 2003 | retrospective (672: 212 M/R, 460 controls) | M/R CVC                               | CRBSI in BMT (M/R) versus leukaemia (no M/R) | MIC (CLSI) 8/12 patients with MIC tested to BMT cultures were resistant to M, R or both: 3/5 control; 2/2 M/R; 3/5 heparin |
| Gilbert et al., 2016     | RCT (1485: 502 controls, 486 M/R, 497 heparin) | M/R CVC                               | CRBSI in control versus M/R versus hep CVC | varied by centre (MIC) Mean M and R MIC of SE from M/R catheter was lower than control catheter; no difference in MIC from skin cultures before insertion versus removal |
| Hanna et al., 2004       | RCT (356: 182 M/R, 174 controls) | M/R CVC                               | MIC for organisms cultured from catheter and/or skin at insertion site | MIC microbroth dilution of M/R catheter was lower than control catheter; no difference in MIC from skin cultures before insertion versus removal |
| Raad et al., 1997        | RCT (298: 151 controls, 147 M/R) | M/R CVC                               | Colonization or CRBSI control versus M/R; ZOI with new M/R CVC from all organisms from colonized CVC; MIC (M, R) for SA, SE from M/R CVC versus insertion site | ZOI of new M/R CVC; MIC microbroth dilution of SA or SE from M/R CVC and insertion site remained at ≤2 mg/L |
| Ramos et al., 2011       | retrospective (4732 isolates: 2451 pre, 2281 post) | M/R CVC                               | Susceptibility of SA, SE to tetracycline and R prior to M/R (1999) and 7 years after use of M/R CVC (2006) | MIC (CLSI) Decrease in percentage of SA and SE resistant to tetracycline or R after 7 years of M/R CVC use; all decreases were significant except R resistance in SA |
| Turnbull et al., 2018    | retrospective (9703 isolates: 2818 pre, 6885 post) | M/R CVC                               | Susceptibilities of SA to tetracycline and R in ICU prior to and after use of M/R CVC | Rate of R and tetracycline resistance unchanged prior to and after use of M/R CVC |

After contact with the device, which of the following does the study show: (i) no change in resistance; (ii) selection for tolerant strains; or (iii) development of new resistance.
exposure to a device containing minocycline, rifampicin or chlorhexidine results when, as a consequence of prior exposure, organisms have different innate susceptibilities to particular antimicrobial agents or combinations. This is not an adaptive response but rather a separation of low-susceptibility strains from high-susceptibility ones based on their ability to tolerate the presence of threshold concentrations of minocycline, rifampicin, chlorhexidine or combinations thereof. Based on finite doses of antimicrobial agents on devices, tolerant organisms (higher MICs) will be able to survive and colonize antimicrobial devices before highly susceptible organisms (lower MICs) can. Differences in tolerance can explain why some organisms are able to break through and colonize antimicrobial devices before others are able to, as well as why organisms can preferentially colonize devices with one combination of antimicrobial agents versus a different combination. The selection of tolerant strains following exposure to an antimicrobial device is not indicative of development of antimicrobial tolerance nor indicative of development of new antimicrobial resistance unless, prior to exposure to the antimicrobial agents on the device, the organisms were susceptible to those agents.

**Single antimicrobial agent device studies**

**Rifampicin alone**

Four *in vitro* studies[^19][^20][^34][^35] reported that devices containing rifampicin alone exhibited newly developed resistance following exposure. The culprit organism was SE in these studies and...
resistance was assessed through increases in MICs following exposure. Several in vivo studies assessed rifampicin devices; however, most did not assess development of new resistance. Two studies on soaked vascular grafts reported no changes in resistance for *Staphylococcus aureus* (SA) or MRSA but one study reported development of new resistance for SE. One human study evaluating vascular grafts soaked in rifampicin reported recurrent breakthrough infections in two patients with two rifampicin-resistant SE and with MRSA. These results were consistent with selection for rifampicin-resistant strains but it is not possible to determine whether exposure to the rifampicin grafts induced newly developed resistance or whether the rifampicin resistance was pre-existing.

Resistance to rifampicin has been reported by occurrence of single point mutations in the β-subchain of bacterial RNA polymerase. These point mutations so impair rifampicin binding and subsequent inactivation of bacterial RNA polymerase that the MIC increases to greater than the limit of testing (i.e. resistant). Point mutations have the greatest likelihood of spontaneously arising and being selected for when a bacterial population is in the presence of rifampicin alone since they involve changes to only a single amino acid. Consequently, development of new resistance has been repeatedly observed and use of rifampicin alone appears unsafe. If other antimicrobial agents are present, they can continue to inhibit or kill bacteria even with favourable RNA polymerase mutations, so rifampicin-resistant bacterial populations might not be able to survive or propagate in the presence of rifampicin in combination with other antimicrobial agents.

### Minocycline alone

One *in vitro* study reported no development of new resistance following repeated exposure to devices containing minocycline alone. No *in vivo* or human studies were conducted on devices containing minocycline alone. Minocycline resistance has been reported to occur through expression of efflux pumps and less commonly through expression of ribosomal protection proteins. In contrast to rifampicin, these types of resistance require acquisition of new genes and expression of new proteins, which are less probable than the occurrence of point mutations. Similarly, bacteria that do acquire minocycline efflux pump or ribosomal protection protein genes when in the presence of minocycline with other antimicrobial agents might not be able to survive and propagate in the presence of the combination because of the antimicrobial activity of the other agent.

### Chlorhexidine alone

Eight *in vitro* studies assessing devices with chlorhexidine alone reported no change in resistance following exposure. One *in vitro* study reported development of new resistance.

| **Table 4. Quality assessment** |
|--------------------------------|
| **In vitro studies** | **In vivo studies** | **Clinical studies** |
| citation | quality score | method | citation | quality score | method | citation | quality score | method |
| Modak, 1992 | 14/19 | A | Avramovic, 1991 | 19/23 | C | Maki, 1997 | 11/14 | C |
| Bergamini, 1996 | 16/19 | B | Sardelic, 1995 | 18/23 | A | Roed, 1997 | 14/14 | B |
| Garrison, 1997 | 14/19 | A | Garrison, 1997 | 21/23 | A | Darouiche, 1999 | 11/14 | B |
| Sampath, 2001 | 14/19 | B | Bandyky, 2001 | 10/12 | D | Wright, 2001 | 8/12 | B |
| Norton, 2001 | 13/19 | C | Chatzinikolaou, 2003 | 11/12 | A | Chatzinikolaou, 2003 | 13/14 | B |
| Tambo, 2001 | 15/19 | B | | | | Hanna, 2004 | 12/14 | B |
| Martro, 2003 | 16/19 | B | | | | Schuerer, 2007 | 9/12 | D |
| Arestrapur, 2004 | 18/19 | A | | | | Timsit, 2009 | 9/14 | B |
| Munson, 2004 | 16/19 | A | | | | Batra, 2010 | 8/12 | A |
| Bayston, 2009 | 17/19 | A | | | | Lee, 2011 | 11/13 | B |
| Skovgaard, 2013 | 16/19 | A | | | | Ramos, 2011 | 10/12 | A |
| Johnson, 2013 | 14/19 | B | | | | Ho, 2012 | 12/13 | B |
| Apisarnthanarak, 2014 | 11/19 | B | | | | Soma, 2012 | 8/12 | A |
| Suwanantar, 2014 | 18/19 | A | | | | Schlett, 2014 | 10/14 | A |
| Wesgate, 2016 | 15/19 | A | | | | Mendoza-Olazaran, 2014 | 10/12 | A |
| Ekizoglu, 2016 | 16/19 | B | | | | Chung, 2015 | 8/12 | B |
| Berard, 2019 | 16/19 | A | | | | McNeil, 2016 | 8/12 | B |
| Rosenblatt, 2019 | 13/19 | A | | | | Gilbert, 2016 | 12/14 | C |

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experimental design assessed MICs of colonizing organisms following exposure to chlorhexidine wipes. The results of a significant increase in prevalence of reduced chlorhexidine susceptibility following chlorhexidine exposure are consistent with selection for more tolerant strains. Insufficient information was provided to determine whether the exposure induced new chlorhexidine resistance or whether the reduced susceptibility was pre-existing prior to the exposure. No in vivo studies with devices containing chlorhexidine alone assessed development of new resistance. Two human studies38,41 reported selection for chlorhexidine-tolerant strains following chlorhexidine exposure and nine studies19,22,24,26,28,51,58 reported no changes in resistance. Chlorhexidine resistance has been reported to be due to the presence of efflux pumps,29 requiring acquisition of new genes and expression of new proteins. Development of new chlorhexidine resistance appears to be rare but continued surveillance is warranted.

**Antimicrobial combination device studies**

**M/R device studies**

Two in vitro studies34,35 on combination M/R devices reported development of new resistance to SE and *Escherichia coli* (EC). The increases in MIC for the combination were modest (4–16-fold) and were much lower than increases in rifampicin MICs (25 000-fold) following exposure to devices containing rifampicin alone. In practical terms, in one of the studies15 the M/R MIC for one strain of SE was reported to increase from 0.02 to 0.25 mg/L following exhaustive sequential passaging at subinhibitory concentrations and for another strain it increased from 0.015 to 0.25 mg/L. These ultimate MICs remain below the CLSI thresholds for susceptibility for minocycline (less than or equal to 4 mg/L) and rifampicin (less than or equal to 1 mg/L);36 thus, while drift of MICs against the combination plausibly occurred, its clinical relevance was more theoretical (as a tolerance shift) than practical because the organisms remained within the therapeutic susceptible range and thus the MIC drifts reported for the SE strains were not clinically relevant. Similarly, the other study34 reported an MIC increase for SE from 0.02 to 0.31 mg/L and for EC from 0.25 to 1 mg/L. Again, the drift in MIC went from very susceptible to susceptible, reflecting increased antimicrobial tolerance; however, the clinical relevance was more theoretical than practical as the organisms remained susceptible and thus the tolerance shift was not clinically relevant, because the culprit organisms remained susceptible to M/R combinations. Additionally, the development of new resistance against the M/R combination for SA was refuted by two independent studies. Since minocycline and rifampicin act with different mechanisms of action at entirely different places in microbial cells, the combination does appear to decrease the likelihood of development of newly resistant organisms, particularly over devices containing rifampicin alone, because two completely different resistance mechanisms would need to simultaneously emerge in the target cells.75,76

**CHXSS device studies**

Although silver sulfadiazine is not a component of the proposed M/R/CH catheter, studies on development of new resistance to CHXSS are included in this review to assess the potential for resistance to emerge against chlorhexidine combinations. No change in resistance was reported in three in vitro studies.22,34,35 No in vivo studies assessed development of new resistance following exposure to CHXSS. Three human studies reported no change in resistance.53,60,61 One human study38 reported selection of more tolerant MRSA strains following exposure to CHXSS; however, this finding was entirely based on genetic analysis (i.e. more isolates contained qacA/B efflux pump genes) and more clinically significant measurement of increases in MICs were not performed. It appears there is a theoretical potential for chlorhexidine resistance to develop but it has been unlikely and has not been clinically widespread or confirmed, particularly when chlorhexidine antimicrobial combinations have been present.

**M/R/CH device studies**

One in vitro study assessed the potential for development of resistance with repeated exposure to subinhibitory concentrations of M/R/CH.33 Organisms with high susceptibility to individual agents as well as low susceptibility to individual agents showed no development of resistance over 20 passages. Only one carbapenem-resistant *Enterobacter* showed a 4-fold increase in MIC during the 20 passages. While there was an increase in MIC, the increase was still well below clinical relevancy. Additionally, after the stressor (M/R/CH) was removed and the organism was passaged in broth alone, the MIC returned to baseline, indicating a phenotypic adaptation rather than development of new resistance. Further, for Gram-positive pathogens common to catheter infections, M/R/CH was highly effective. In the first few passages, subinhibitory concentrations were established for a few SA and SE; however, within two passages, the organisms died and passages could not continue. Based on this study and previous drug combination studies, with the addition of the third component
(chlorhexidine) to M/R there is no evidence of the potential for new resistance developing after exposure.

**Conclusions**

A systematic literature review was undertaken to assess evidence for the development of new antimicrobial resistance from exposure to medical devices containing rifampicin, minocycline, chlorhexidine or their combinations. Strengths of this study include: a search strategy that was conducted in multiple databases; use of systematic criteria to select studies and abstract data from these studies, thus reducing potential for selection bias; and use of standardized metrics for assessing the quality of studies. Limitations include: while multiple databases were searched, we did not include conference abstracts or search grey literature for additional studies; manuscripts included were limited to English language; and variability in the quality of studies. While the majority of our studies were scored as ‘high quality’ there were a few studies that did not present detailed methods or criteria and were scored as ‘low quality’ and should not be compared with equal weight.

Resistance was most likely to emerge in devices containing rifampicin as a single antimicrobial agent because only a single point mutation in RNA polymerase was required for rifampicin resistance to emerge. Development of rifampicin resistance was seen in multiple studies. In contrast, development of new resistance to minocycline or chlorhexidine single-agent devices was much less likely because acquisition of genes and expression of new proteins was required for new resistance to develop. Clinically meaningful development of new resistance against minocycline or chlorhexidine in devices was not confirmed in human studies although slight drifts in MICs were observed.

Emergence of new resistance to double combinations of M/R or CHXSS, although theoretically possible, was rarer and no clinical trials confirmed its occurrence and some refuted it. Studies did demonstrate that selection of more tolerant isolates capable of colonizing devices occurred when testing was performed on these combinations, but the lower innate susceptibilities of the tolerant strains likely existed prior to the exposure. The risk of development of new resistance to these antimicrobial combinations appears more fear-based rather than substantiated by clinical and experimental evidence but warrants continued surveillance.

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**Supplementary data**

The Reviewer report is available as [Supplementary data](https://jac-american-opioid-crit.pdf) at JAC-AMR Online.

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