

Summary Report

Mupirocin

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks
List
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Frequently Used Abbreviations

| | |
|------|--|
| API | Active Pharmaceutical Ingredient |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| IRB | Institutional Review Board |
| MRSA | Methicillin-resistant <i>Staphylococcus aureus</i> |
| MIC | Minimum inhibitory concentration |
| OTC | Over-the-counter |
| ROA | Route of administration |
| SME | Subject matter expert |
| SSTI | Skin and soft tissue infection |
| UK | United Kingdom |
| US | United States |

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of mupirocin (UNII code: D0GX863OA5), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how mupirocin is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and health care practitioners were consulted to identify how mupirocin has been used historically and currently.¹⁻³ Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.^{1,4,5} Rather, the aim was to summarize the available evidence on the use of mupirocin and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Mupirocin was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Sincerus, and Triangle Compounding Pharmacy. Mupirocin was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Mupirocin was nominated for the treatment of superficial skin infections, nasal infections and wounds via topical cream, gel, ointment, solution and suspension, nasal spray, and otic preparations in concentrations ranging from 0.2 to 5%. The nomination seemed to indicate that the otic ROA was for veterinary use only.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of mupirocin.⁶⁻¹⁵

Reasons provided for nomination to the 503B Bulks List included:

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Need for accuracy; individual finished products have a considerable variance in the actual APIs, and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication,
- FDA-approved drug product not available in liquid form for nasal or otic administration.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of mupirocin products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the

medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for mupirocin; name variations of mupirocin were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing mupirocin. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe two concepts: mupirocin, and nasal or otic administration or form. The second search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: mupirocin; topical administration or form; and substances nominated for use in combination with (refer to Appendix 1 for full search strategies). A literature review was not conducted for topical single-ingredient mupirocin products due to the availability of FDA-approved single-ingredient mupirocin products for this ROA. Results were limited to human studies in English language. Searches were conducted on February 18, 2021. In addition, the ECRI Guidelines Trust[®] repository was searched on February 18, 2021 for clinical practice guidelines that recommended the use of mupirocin and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The deduplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which mupirocin was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if mupirocin was used as current or discontinued FDA-approved product in the nominated dosage form, ROA, or combination; unspecified dosage form or ROA; or a dosage form or ROA that was not nominated. Studies in which mupirocin was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and

put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of mupirocin; setting; total number of patients; number of patients who received mupirocin; patient population; indication for use of mupirocin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of mupirocin in a combination product; use and formulation of mupirocin in a compounded product; use of mupirocin compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances mupirocin was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use mupirocin. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of mupirocin in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted for the project Year 3 surveys.

The survey was posted on the project website, and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Mupirocin is available as an FDA-approved product in the nominated dosage form and ROA.
- Mupirocin was available as an FDA-approved 2% nasal ointment (Bactroban) that was discontinued, not for reasons of safety or efficacy.
- Mupirocin is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for mupirocin.
- Mupirocin is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia and the UK. Mupirocin is available as an OTC product in Canada.

Table 1. Currently approved products – US^a

| Active Ingredient | Concentration | Dosage Form | Route of Administration | Status | Approval Date^b |
|--------------------------|----------------------|--------------------|--------------------------------|---------------|----------------------------------|
| Mupirocin | 2% | Ointment | Topical | Prescription | 12/4/2002 |
| Mupirocin calcium | 2% | Cream | Topical | Prescription | 1/24/2013 |

^aSource: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions^a

| Active Ingredient | Concentration | Dosage Form | Route of Administration | Approved for Use | | |
|-------------------|---------------|-------------|-------------------------|------------------|--------------------------------|----------------------------|
| | | | | Country | Status | Approval Date ^b |
| Mupirocin | 2% | Ointment | Topical | Abu Dhabi | Active | – |
| | | | | Australia | Prescription-only medicine | 8/14/1991 |
| | | | | Belgium | Medical prescription | 6/10/1986 |
| | | | | Hong Kong | Prescription-only medicine | 1/15/1987 |
| | | | | Ireland | Prescription-only nonrenewable | 4/29/1986 |
| | | | | Namibia | – | 12/28/1986 |
| | | | | New Zealand | Prescription | 7/18/1985 |
| | | | | Saudi Arabia | Prescription | – |
| | | | | UK | Prescription-only medicine | 3/26/1985 |
| Mupirocin | 2% | Cream | Topical | Abu Dhabi | Active | – |
| | | | | Australia | Prescription-only medicine | 4/23/1988 |
| | | | | Namibia | – | 12/28/2003 |
| | | | | UK | Prescription-only medicine | 10/28/1998 |

| | | | | | | |
|-----------|----|----------|-------|----------------|--------------------------------|------------|
| Mupirocin | 2% | Ointment | Nasal | Abu Dhabi | Active | – |
| | | | | Australia | Prescription-only medicine | 8/14/1991 |
| | | | | Belgium | Medical prescription | 12/16/1992 |
| | | | | Hong Kong | Prescription-only medicine | 5/29/1990 |
| | | | | Ireland | Prescription-only nonrenewable | 7/17/1989 |
| | | | | Namibia | – | 1/1/1989 |
| | | | | Saudi Arabia | Prescription | – |
| | | | | United Kingdom | Prescription-only medicine | 3/7/1988 |

Abbreviations: –, not provided

^aMedicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 1940 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1286 titles and abstracts were screened. After screening, the full text of 402 articles was reviewed. Finally, 5 studies were included. Three hundred ninety-seven studies were excluded for the following reasons: wrong study design (185 studies); mupirocin used as an FDA-approved product (100); mupirocin used as an unspecified formulation (96); mupirocin used in a formulation that was not nominated (7); mupirocin only mentioned briefly (3); unable to obtain full text (3); language other than English (2); wrong substance (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 5 included studies were published between 2006 and 2019. There were 2 experimental studies, 0 observational studies, 3 descriptive studies, and 0 clinical practice guidelines. The 5 studies were conducted in the following countries: Australia, Malaysia, and the US.

A total of 87 patients participated in the 5 included studies. The number of patients in each study ranged from 2 to 25.

Outcome measures differed among the included studies and included Sino-Nasal Outcome Test (SNOT), nasal endoscopy score, microbial culture, resolution of symptoms.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of mupirocin

Forty patients received mupirocin as an experimental treatment for *Staphylococcus aureus*-associated chronic rhinosinusitis administered as a nasal lavage or nasal gel and nebulization twice a day (nasal lavage and nebulization) or once a week (nasal gel). Duration of treatment ranged from 4 to 6 weeks. Ten patients received mupirocin as an experimental treatment after endoscopic endonasal surgery for skull base lesions administered as a nasal lavage three times a day for 4 weeks. Two patients received mupirocin as an experimental treatment for empty nose syndrome administered as a nasal solution at an unknown frequency and duration.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Mupirocin was used in a combination product and as a compounded product (refer to Tables 8 and 9).

In 4 studies, the authors' concluding statement recommended the use of mupirocin for the treatment of *Staphylococcus aureus*-associated chronic rhinosinusitis or to reduce sinonasal morbidity after endoscopic endonasal surgery.¹⁶⁻¹⁹ In 1 study, the authors' conclusions did not address the use of mupirocin.²⁰ Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

Additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of mupirocin.

Mupirocin is a unique antibiotic that was first derived from *Pseudomonas fluorescens* by Fuller et al. in 1971.²¹ Reports of the antimicrobial effects of *Pseudomonas fluorescens* were noted as far back as 1887.^{12,21} Fuller et al. proposed the name pseudomonic acid for the parent monocarboxylic acid that they isolated.²¹ The substance known today as mupirocin is a mixture of 4 pseudomonic acids (A, B, C and D) in which pseudomonic acid A predominates, comprising 90% to 95% of the mixture.^{22,23} Mupirocin inhibits bacterial protein synthesis by binding to bacterial isoleucyl-tRNA synthetase, thereby halting polypeptide chain elongation at sites where isoleucine needs to be inserted.^{22,24,25} Mupirocin is active against gram-positive bacteria, in particular *Staphylococci* (including methicillin-resistant *Staphylococcus aureus*, MRSA) and *Streptococci*, and certain gram-negative bacteria, such as *Hemophilus influenzae* and *Neisseria gonorrhoeae*.²⁴ Mupirocin is a bactericidal at concentrations achieved with topical or nasal administration.²⁶⁻²⁸ No measurable systemic absorption or mupirocin was detected in healthy subjects with topical administration with occlusive dressings.^{26,28,29} When administered orally or intravenously, mupirocin is rapidly broken down (elimination half-life 20 to 40 minutes) to the inactive metabolite, monic acid, which is predominantly eliminated via the kidneys.^{29,30} This rapid metabolism with oral or parenteral administration limits the use of mupirocin to topical or nasal administration. Parenti et al. suggested that many of the properties of mupirocin, namely its unique structure and mechanism of action, activity against common skin pathogens, and negligible systemic absorption, make it the ideal topical antibiotic.¹² Indeed, Tucaliuc et al. called mupirocin “the world’s most widely used topical antibiotic for treating infections of soft tissue and skin with methicillin-resistant *Staphylococcus aureus* or to decolonize patients at risk with this bacterium.”²³

Early studies described the use of topical mupirocin to treat primary skin infections, such as impetigo, ecthyma and furunculosis.³¹ Mupirocin is currently available as an FDA-approved topical ointment and cream labeled for the treatment of impetigo and infected traumatic skin lesions, respectively.^{26,28} Impetigo is a bacterial infection of the skin, seen most commonly in young children, caused by *Staphylococcus aureus* and/or β -hemolytic *Streptococci*.^{32,33} Ecthyma is a deeper infection of the skin, also typically caused by *Staphylococcus aureus* and/or β -hemolytic *Streptococci*, which occurs more commonly in immunocompromised individuals.^{32,33} In a 2012 review of bacterial skin and soft tissue infections (SSTIs), the authors stated that uncomplicated superficial SSTIs, such as impetigo, could often be managed with topical therapy alone, providing oral antibiotics only if necessary.³³ The authors of this review recommended topical mupirocin or fusidic acid for treating impetigo. The 2014 Infectious Diseases Society of America practice guidelines for the diagnosis and management of SSTIs recommended topical mupirocin or retapamulin ointment (twice a day for 5 days) in patients with impetigo who have a limited number of lesions (strong recommendation, high level of evidence).³² Oral antibiotics were recommended for patients with impetigo who had numerous lesions or if multiple people were affected, in order to reduce transmission of the infection. Oral antibiotics were also recommended for patients with ecthyma. The 2011 Infectious Diseases Society of America practice guidelines on the treatment of MRSA infections in adults and children also recommended topical mupirocin ointment for children with minor skin infections, such as impetigo, or secondarily infected skin lesions.³⁴

Mupirocin has also been proposed for use in the management of acute or chronic wounds, although there is limited evidence to support such use. Topical antibiotics offer several advantages in wound care, including high and sustained local concentration of drug at the site of infection; limited systemic absorption and therefore, systemic adverse effects; possibility of avoiding the use of systemic antibiotics; ability to use novel drugs not available for systemic administration; ease of application in an outpatient setting; and need for frequent administration directing patient and caregiver attention to

the wound.³⁵ The need for frequent administration of topical antibiotics can also be a drawback to their use, along with the difficulty of dosing accurately, limited penetration restricting use to superficial wounds without cellulitis, possible disruption of wound healing, potential for systemic absorption with large wounds and local hypersensitivity in some patients.³⁵ Most wounds with signs of infection (erythema, edema, warmth, pain, exudate and/or malodor) should be treated with systemic antibiotics.^{35,36} Topical antibiotics may be used as an adjunctive therapy in patients with infected wounds, particularly in certain situations, such as poorly vascularized wounds (eg, burn wounds), wounds with biofilms, or infection with multidrug-resistant organisms.³⁵ The principal arguments against the use of topical antibiotics in wound management are the lack of evidence from clinical trials supporting their use, no accepted standardized methods to evaluate their efficacy, and persistent concerns about their potential to delay wound healing.³⁵

A 2017 Cochrane review on topical antimicrobial agents for treating foot ulcers in patients with diabetes found very few studies, with most of these being poorly designed trials on this topic.³⁷ Comparing topical antimicrobial treatments (nondressings) to topical nonantimicrobial treatments (nondressings), the 4 included studies with a total of 132 participants provided low- to very low-certainty evidence and the 95% confidence intervals for the outcome measures spanned benefit and harm. Comparing different topical antimicrobial treatments with one another, the 8 included studies with a total of 250 participants provided very low-certainty evidence and the available outcome data was limited. Comparing topical antimicrobial treatment to systemic antibiotics, the 4 included studies with a total of 937 participants provided very low-certainty evidence on the effect of these therapies on wound healing, resolution of infection and need for surgical resection. Overall, the authors were only able to suggest that antimicrobial dressings may increase the number of diabetic foot ulcers healed over time compared to nonantimicrobial dressings, and there is probably little difference in the incidence of adverse effects between topical and systemic antibiotics. The 2019 update of the guidelines on the diagnosis and treatment of foot infection in persons with diabetes from the International Working Group on the Diabetic Foot recommended the following: for patients with a severe diabetic foot infection, initially parenteral antibiotic therapy, then oral antibiotic therapy; for most patients with a moderate infection, oral antibiotic therapy (or initial parenteral antibiotic therapy, then oral); and for patients with a mild infection, oral antibiotic therapy.³⁸ The recommendation for severe diabetic foot infections was considered strong with a low level of evidence while the recommendations for moderate and mild infections were considered weak and also with low levels of evidence. The authors of the guideline “suggest not using any currently available topical antimicrobial agent for treating a mild diabetic foot infection” (weak recommendation, moderate level of evidence).³⁸ They acknowledged the theoretical benefits of topical therapy, including lower cost and reduced exposure to systemic antibiotics and therefore, fewer adverse events and opportunities for development of antibiotic resistance. However, the authors stated that no published studies supported the use of topical antimicrobial therapy either alone (for mild infections) or in combination with systemic antibiotics (for moderate infections) for the treatment of diabetic foot infections.

Three articles were found that described the use of mupirocin in topical combination products but did not meet the inclusion criteria. In a case series published in 2017, one patient with traumatic wounds on both elbows was prescribed a topical anhydrous silicone base compounded with pracaxi oil and mupirocin.³⁹ This preparation was applied 3 times a day; after 11 days, the wounds had healed completely and the patient reported rapid improvement from baseline. Two articles provided formulations for compounded nipple ointments with mupirocin for use in women with sore, cracked, and/or painful nipples due to breastfeeding.^{40,41} The author of one of these articles attributed the development of this “all-purpose nipple ointment” to a Canadian pediatrician, Jack Newman, whose

original formulation contained mupirocin 2% ointment (15 g), betamethasone 0.1% ointment (15 g) and miconazole powder (final concentration 2%).⁴¹ Mupirocin was included in the formulation to help prevent or treat bacterial infection and because it would be rapidly metabolized if ingested orally by the suckling infant. Betamethasone was included for its anti-inflammatory properties and miconazole for its antifungal properties. This article provided three additional formulations for an all-purpose nipple ointment, submitted by compounding pharmacists.⁴¹ The first formulation contained mupirocin 2% ointment 22 g (final concentration 1%), betamethasone dipropionate 0.022 g (0.05%), miconazole 0.88 g (2%) and yellow color 2% solution in Aquaphor ointment. The second formulation contained mupirocin 2% ointment 25 g (final concentration 0.5%), betamethasone valerate 0.1% ointment 25 g (0.025%), nystatin 100,000 U/g ointment 25 g (25,000 U/g) and clotrimazole 1% cream 25 g (0.25%). The third formulation contained mupirocin 2% ointment 15 g (final concentration 0.5%), betamethasone valerate 0.1% ointment 15 g (0.025%), nystatin 100,000 U/g ointment 15 g (25,000 U/g), clotrimazole 1.5 g (2.5%) mixed with ethoxydiglycol reagent 0.5 mL in Aquaphor ointment. Allen published a formula for a nipple ointment with mupirocin 1 g, betamethasone acetate 100 mg and nystatin 1 g in hydrophilic petrolatum.⁴⁰ One in vitro study was found describing the formulation and testing of a mupirocin 2% spray.²⁵ The spray was effective against *Escherichia coli* growth and biofilm formation and nontoxic to fibroblast cells. The authors suggested that a spray formulation might be preferable to commercially available topical mupirocin ointment or cream because it is easy to apply and covers wounds with a protective film without the need for dressings.

Several studies have explored the use of mupirocin for the prevention or treatment of otorrhea.^{8,42,43} Otorrhea is the most common postoperative complication of tympanostomy tube placement.⁸ In children less than 3 years of age, otorrhea is typically caused by *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis*; in older children or those who have received antibiotics, *S aureus* and *Pseudomonas aeruginosa* are the most common causative agents.⁸ As community-acquired MRSA skin and respiratory infections have become more prevalent, so too has MRSA otorrhea.⁸ Only a few medications are FDA-approved for use in patients with perforated tympanic membranes and/or tympanostomy tubes.⁴⁴ Most of these medications are fluoroquinolone antibiotics, which are effective against the microorganisms that typically cause otorrhea but are expensive and have an unnecessarily broad spectrum of activity.⁴⁴ Systemic fluoroquinolones are not recommended as monotherapy for invasive MRSA infections due to resistance to this class of antibiotics.⁸ Although high concentrations of fluoroquinolones are achieved with local topical administration for otorrhea, these medications fail to resolve more than 50% of cases of MRSA-associated tympanostomy tube otorrhea.^{8,44} In a 2008 randomized study from Japan, Furukawa et al. evaluated the effectiveness of topical mupirocin ointment versus ofloxacin ear drops for the treatment of MRSA otorrhea in patients with chronic otitis media with perforation or postoperative patients.⁴² Mupirocin ointment was applied at a clinic by a physician to the tympanic membrane and promontory around and through the perforation 1 to 4 times (average 2.3 times) for 2 to 3 weeks. Sixteen patients (18 ears) received mupirocin and 10 patients (10 ears) received ofloxacin. Otorrhea was completely cured in all patients receiving mupirocin (18/18 ears, 100%) and 2 patients receiving ofloxacin (2/10 ears, 20%). The 8 patients who were not cured with ofloxacin administration subsequently received mupirocin, which resolved the otorrhea in all of these patients. The authors hypothesized that when administered in and around the tympanic membrane, the mupirocin ointment is effective because it is softened, melted, and thereby easily delivered to the middle ear and eliminates MRSA from the external ear canal. The authors concluded “We demonstrated a perfect and complete elimination of MRSA otorrhea, without deterioration of hearing, by using a minimally essential ototopical application of mupirocin ointment, thus indicating the first-line therapy for MRSA otorrhea.”⁴² In 2012, Park and Lee described the use of mupirocin-coated tympanostomy tubes in 67 patients (98

ears) with chronic middle ear effusion or atelectatic otitis media.⁴³ The tubes were coated with mupirocin ointment at the time of placement and no otic drops were prescribed during the immediate postoperative period. Early postoperative tympanostomy tube otorrhea occurred in only one patient, suggesting that coating the tympanostomy tube with mupirocin ointment at the time of surgery was an effective preventative measure against postoperative otorrhea. In 2018 Yankey and Isaacson (and later, in 2020, Isaacson alone) described a protocol in which children with MRSA tympanostomy tube otorrhea received aural suctioning, culture-directed systemic antibiotics and fluoroquinolone ear drops (if cultured MRSA sensitive to them); topical mupirocin ointment was introduced into this protocol in 2014.^{8,44} A single 1-mL dose of mupirocin 2% ointment was applied to the tympanostomy tube, tympanic membrane and external auditory canal with a 3-mL syringe and 18-gauge catheter under microscopic guidance. Yankey and Isaacson reported that between 2001 and 2017, 21 children (25 ears) received the standard protocol and 8 children (12 ears) received the protocol with adjunctive topical mupirocin.⁸ In some cases, the topical mupirocin was mixed with triamcinolone 0.1% cream. According to the authors, “MRSA otorrhea was eventually controlled in all children in both groups.”⁸ Recurrence of MRSA tympanostomy tube otorrhea in the mupirocin and control groups occurred in 0 of 12 ears (0%) and 10 of 25 ears (40%), respectively. However, the mean duration of follow-up was longer in the control group (24 months) than it was in the mupirocin group (7 months). Recurrence of nonMRSA tympanostomy tube otorrhea in the mupirocin and control groups was 6 of 12 ears (50%) and 9 of 25 ears (36%), respectively. The authors concluded that topical mupirocin ointment “delivers a high dose and effective agent for several days duration” and acknowledged that its role in the management of MRSA tympanostomy tube otorrhea requires further investigation.⁸

Topical mupirocin cream or ointment is also used to prevent infection in patients on hemodialysis or peritoneal dialysis. These patients are at risk for developing catheter exit-site infections, which may progress to peritonitis and/or bacteremia.^{45,46} Such infections may lead to failure of the technique (requiring catheter removal or replacement), hospitalization and increased mortality.⁴⁵ Mupirocin is a preferred topical antibiotic for the prevention of exit-site infections because it is effective against common gram-positive organisms, such as *S aureus* and *Streptococci*, has few side effects, and is not used as a systemic antibiotic to treat serious infections.^{45,46} Mupirocin is typically applied to the exit site once a day, or each time the dressing is changed.^{45,46} Mupirocin ointment containing polyethylene glycol should not be used in large quantities due to the risk of systemic absorption of the polyethylene glycol or distortion of polyurethane catheters.^{26,47} In a 2010 Cochrane review on interventions to prevent infectious complications in hemodialysis patients with central venous catheters, mupirocin ointment was found to significantly reduce the risk of exit-site infections caused by *S aureus* as well as catheter-related bacteremia.⁴⁶ The authors concluded that “The clinical decision to use mupirocin ointment as a prophylactic agent in the prevention of CVC [central venous catheter] infections requires local knowledge of the prevalence of antibiotic sensitivity within that community.”⁴⁶ A 2017 Cochrane review evaluated the use of antimicrobial agents, administered topically, intranasally, orally or parenterally, for the prevention of peritonitis in patients on peritoneal dialysis.⁴⁵ The review included 39 studies with 4374 patients and found that while intravenous antibiotic administration at the time of catheter placement may reduce the risk of early peritonitis, the use of topical, intranasal or oral antibiotics had “uncertain effects” on the risk of exit-site infection and peritonitis. Overall, the available evidence was of low quality (lacking statistical power, potential for bias) and the authors suggested that additional large randomized controlled trials with sufficient follow-up were needed. The 2011 International Society for Peritoneal Dialysis position statement on reducing the risk of peritoneal dialysis-related infections also considered the use of topical and intranasal mupirocin.⁴⁷ The authors of this statement observed that some dialysis centers obtain nasal cultures prior to catheter placement and treat patients who are positive for *S aureus* carriage with intranasal mupirocin

while others recommend daily application of mupirocin cream or ointment around the catheter exit site. The authors hypothesized that a combination of both of these strategies might be most effective for preventing peritonitis. They recommended that each center decide which approach works best for their patient population and cautioned that “Without a protocol to prevent *S aureus* PD [peritoneal dialysis]-related infections, that organism will be the major cause of exit-site infection, which will often lead to peritonitis and catheter loss.”⁴⁷ In a 2013 review, Segal and Messana noted that while daily topical application of mupirocin had been shown to reduce the incidence of exit-site infection and peritonitis in several controlled studies, mupirocin is not effective against gram-negative organisms, such as *Pseudomonas aeruginosa*.⁴⁸ The authors recommended that facilities adhere to good hygiene practices when placing and maintaining dialysis catheters, including cleansing exit sites with topical antiseptics, and use topical mupirocin or gentamicin in patients with documented *S aureus* colonization or who are at high risk of colonization and infection, such as patients with diabetes mellitus or who are immunocompromised. Both Segal and Messana and the authors of the International Society of Peritoneal Dialysis statement suggested that based on clinical experience with mupirocin (and antibiotics in general), long-term use of mupirocin in individual patients and/or widespread use of mupirocin may lead to increased resistance to this drug.^{47,48}

In addition to being administered topically, mupirocin has been used intranasally for *S aureus* decolonization since the 1980s.⁴⁹ Mupirocin has also been used as a nasal irrigation solution in patients with chronic rhinosinusitis.⁵⁰⁻⁵² Topical mupirocin ointment was first approved for use in the US in 1987; due to isolated reports of stinging and burning with mucosal application, this product was not recommended for nasal use.^{26,53} The more stable calcium salt of mupirocin was used to formulate an ointment for intranasal use, which was approved by the FDA in 1995.⁵³ Mupirocin 2% nasal ointment (Bactroban®) was discontinued by the manufacturer in 2020.⁵⁴ Allen provided a formulation for a compounded mupirocin 1% suspension to be administered as a nasal spray or drop.⁵⁵ *S aureus* asymptotically colonizes the nose of approximately 30% of the human population, either transiently or persistently.⁵⁶⁻⁵⁸ Some populations, including patients who are hospitalized, receive peritoneal dialysis or are immunocompromised, have a higher rate of *S aureus* colonization.^{49,56} Patients in whom the normal barriers of the skin are compromised, such as those with atopic dermatitis or burns, also have a higher risk of *S aureus* colonization.⁵⁸⁻⁶⁰ Although *S aureus* does not typically colonize the skin, it is responsible for 76% of all SSTIs.⁵⁸ *S aureus* colonization is a risk factor for SSTIs and bacteremia in the general hospital and intensive care unit populations, patients undergoing surgery, patients on peritoneal dialysis and patients with atopic dermatitis or burns.^{49,59,60}

Nasal mupirocin is often part of a decolonization protocol prior to surgery or placement of a catheter for peritoneal dialysis or hemodialysis. These protocols, which include a prescription for nasal mupirocin ointment, along with other antiseptic measures such as topical chlorhexidine, are prescribed either to all patients undergoing a procedure or only to those patients positive for *S aureus* on nasal culture.⁶¹⁻⁶³ Intranasal mupirocin ointment, typically applied 2 to 3 times a day for 5 days, has been shown to result in successful clearance of *S aureus* (including MRSA) in several populations.^{47,59,60,62,64,65} A 2008 Cochrane review on the effect of nasal mupirocin ointment in patients with *S aureus* colonization on *S aureus* infections included 9 randomized controlled trials with 3396 patients from a variety of populations, including both surgical and nonsurgical patients, and patients on peritoneal dialysis or hemodialysis.⁶⁶ The authors found that nasal mupirocin resulted in a statistically significant reduction in *S aureus* infections. In a 2016 systematic review on preoperative decolonization with nasal mupirocin and topical chlorhexidine, the authors found that this strategy effectively reduced *S aureus*-associated surgical site infections.⁶¹ The 2013 clinical

practice guidelines for antimicrobial prophylaxis in surgery from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society and the Society for Healthcare Epidemiology of America provided detailed recommendations for a variety of surgical procedures, including cardiothoracic, gastrointestinal, gynecological, ophthalmic, orthopedic and neurological procedures.⁶⁷ Preoperative nasal mupirocin was recommended for all patients with documented *S aureus* colonization undergoing cardiac procedures, spinal procedures, hip fracture repair or total joint replacement (strength of evidence: A, evidence from well-conducted randomized controlled clinical trials and/or cohort studies). The authors of these guidelines commented that the preoperative timing and duration of nasal mupirocin administration have been standardized. In 2014, the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, the American Hospital Association, the Association for Professionals in Infection Control and Epidemiology and The Joint Commission published an expert guidance document on preventing surgical site infections in acute care hospitals.⁶⁸ The authors recommended that for high-risk procedures, including some cardiothoracic and orthopedic procedures, hospitals screen patients for *S aureus* and decolonize those with positive cultures with an antimicrobial and/or antiseptic agent (moderate quality of evidence). The authors acknowledged that there was no standardized approach to screening and decolonization, although most clinicians used a combination of nasal mupirocin and topical chlorhexidine gluconate. The 2016 World Health Organization global guidelines for the prevention of surgical site infection recommended that patients with known nasal carriage of *S aureus* undergoing cardiothoracic or orthopedic surgery receive intranasal mupirocin ointment, with or without chlorhexidine gluconate body wash (strong recommendation, moderate quality of evidence).⁶³ The guideline panel also suggested treating patients with known nasal carriage of *S aureus* undergoing other types of surgery with nasal mupirocin, with or without chlorhexidine gluconate body wash (conditional recommendation, moderate quality of evidence). The authors of the 2019 American Academy of Orthopedic Surgeons clinical practice guideline on diagnosing and preventing periprosthetic joint infections provided a consensus opinion based on clinical opinion (in the absence of reliable evidence) “that preoperative nasal mupirocin decolonization is a low-risk, reasonable option prior to hip and knee arthroplasty in patients who are MRSA carriers.”⁶⁹

Nasal mupirocin for *S aureus* decolonization has also been used in other patient populations, such as those with atopic dermatitis, burns, or in neonatal intensive care units.^{59,61,64} In a 2014 before-and-after study, Jaspers et al. described the use of nasal mupirocin in patients with burns.⁵⁹ The study consisted of three periods: the control period in which mupirocin was not used; the first study period in which nasal mupirocin (3 times a day for 5 days) was initiated in all patients admitted to the burn center; and the second study period in which nasal mupirocin was administered to all admitted patients and burn center personnel were screened and treated for nasal *S aureus* colonization. The primary outcome measure was burn wound colonization with *S aureus*. No significant difference in burn wound colonization was detected between the three study groups. The authors suggested that although nasal mupirocin may have eliminated the primary source of *S aureus*, other sites of bacteria on and in the body, such as the groin, axilla, or other parts of the skin, or respiratory and gastrointestinal flora, were not eliminated and therefore, sources of colonization. The authors concluded that “At present, there is insufficient evidence to support the use of nasal mupirocin in routine clinical practice in burn care patients.”⁵⁹ Kotloff et al. evaluated the safety and efficacy of applying topical (periumbilical and perianal) and nasal mupirocin to critically ill infants.⁶⁴ Infants who tested positive for *S aureus* on nasal swab culture were randomized to receive either mupirocin or no treatment. Primary decolonization occurred in significantly more infants in the mupirocin group than in the control group, with 94% (62/66) and 5% (3/64) of the infants in the mupirocin and control groups, respectively, decolonized. Persistent decolonization on day 22 also occurred in significantly

more infants in the mupirocin group than in the control group, with 46% and 2% of infants in the mupirocin and control groups, respectively, persistently decolonized on day 22. Although mupirocin was generally well tolerated, more infants in the mupirocin group experienced rashes (typically mild and perianal) than those in the control group. The authors concluded that “With these findings, it is suggested that in NICUs [neonatal intensive care units] where clinical SA [*Staphylococcus aureus*] infections are prevalent, mupirocin decolonization might reduce the burden of MRSA and MSSA [methicillin-susceptible *Staphylococcus aureus*] and prevent clinical infections.”⁶⁴ The authors observed that many infants who remain hospitalized become recolonized with *S aureus* after 2 to 3 weeks; therefore, after that time, alternative or additional methods for preventing transmission should be explored.

Although nasal mupirocin ointment is an effective agent for *S aureus* decolonization, there are several disadvantages to its use. Krismer et al. suggested that mupirocin’s “rather broad” spectrum of activity “probably damages the entire nasal microbiota.”⁵⁶ The organisms that comprise the nasal microbiota may help inhibit *S aureus* colonization. Krismer et al. also suggested that mupirocin is bacteriostatic and therefore only inhibits *S aureus* growth, although the prescribing information for mupirocin nasal ointment (Bactroban®) indicates that mupirocin is bactericidal at concentrations achieved with intranasal administration.^{27,56} However, mupirocin is highly protein bound and the effect of nasal secretions on the drug is unknown.²⁷ In order to successfully eliminate nasal *S aureus*, mupirocin ointment needs to be administered frequently over several days. Some patients or health care personnel may find this treatment protocol difficult to follow, which may decrease compliance and therefore the success of nasal decolonization. A 2007 retrospective study from Germany evaluated the effectiveness of MRSA eradication procedures, specifically washing patients colonized or infected with MRSA with octenidine dihydrochloride and administering mupirocin ointment intranasally, in everyday clinical working conditions.⁷⁰ MRSA was eradicated (3 consecutive negative swabs) on dismissal in only 6% of the patients (5/87) included in the study; 8% of the patients (7/87) had 2 negative swabs prior to dismissal and 7% of the patients (6/87) had 1 negative swab prior to dismissal. The authors hypothesized that the poor rate of eradication was due, at least in part, to poor compliance with the decolonization protocol. For example, 40 patients had nasal swabs that were positive for MRSA, but only 30 patients received nasal mupirocin. The authors concluded that to ensure good compliance, MRSA isolation and decontamination protocols should be as simple and standardized as possible. The final disadvantage to the use of nasal mupirocin is that several studies have shown that although nasal mupirocin ointment may initially result in *S aureus* decolonization, recolonization is common and repeated and/or long-term use of mupirocin may lead to resistance.⁴⁹

Reports of resistance to mupirocin emerged soon after the ointment was approved for use in countries around the world in the mid-1980s. In two letters published in *The Lancet* in 1987, clinicians from the UK (where mupirocin ointment was authorized for use in 1985) and Italy described mupirocin-resistant *S aureus* isolates from 14 and 12 patients, respectively, on their dermatology wards.^{71,72} Rahman et al., reporting from the UK, noted that 3 of the 14 patients with resistant isolates had received long-term mupirocin therapy ranging in duration from 1 to 9 months.⁷² These clinicians cautioned that such “Long-term therapy should seemingly be avoided, at least in patients admitted to hospital wards, if we are to retain the use of this drug.”⁷² There are generally considered to be 3 categories of mupirocin susceptibility: susceptible at minimum inhibitory concentrations (MICs) <4 mcg/mL; low-level resistance at MICs of 8 to 256 mcg/mL; and high-level resistance at MICs >512 mcg/mL.^{49,73-75} The enzyme upon which mupirocin acts, isoleucyl-tRNA synthetase, is also the target of resistance.⁴⁹ Low-level (chromosome-encoded) mupirocin resistance is due to a point mutation in the native isoleucyl-tRNA synthetase gene, which alters the mupirocin binding site.^{49,73-75} High-level

(plasmid-encoded) mupirocin resistance is conferred by the acquisition of the plasmid-borne genes, *mupA*, which encodes a “eukaryotic-like”⁷³ t-RNA synthetase that does not bind mupirocin, or *mupB*.^{49,74,75} Coresistance to other antibiotics, including gentamicin, tetracyclines and macrolides, may be located on the same plasmid as *mupA*.⁷⁴ Both low- and high-level mupirocin resistance are associated with failure of MRSA decolonization.⁷⁴ The clinical relevance of low-level resistance has yet to be fully elucidated because high concentrations of mupirocin can be attained with topical or nasal application. However, “even low-level mupirocin resistance in *S. aureus* may have implications for individual patients and hospitals, as it may lead to decolonization failure leaving the patient at increased risk for developing an endogenous *S. aureus* or MRSA infection or allowing transmission of strains to other patients.”⁷⁴

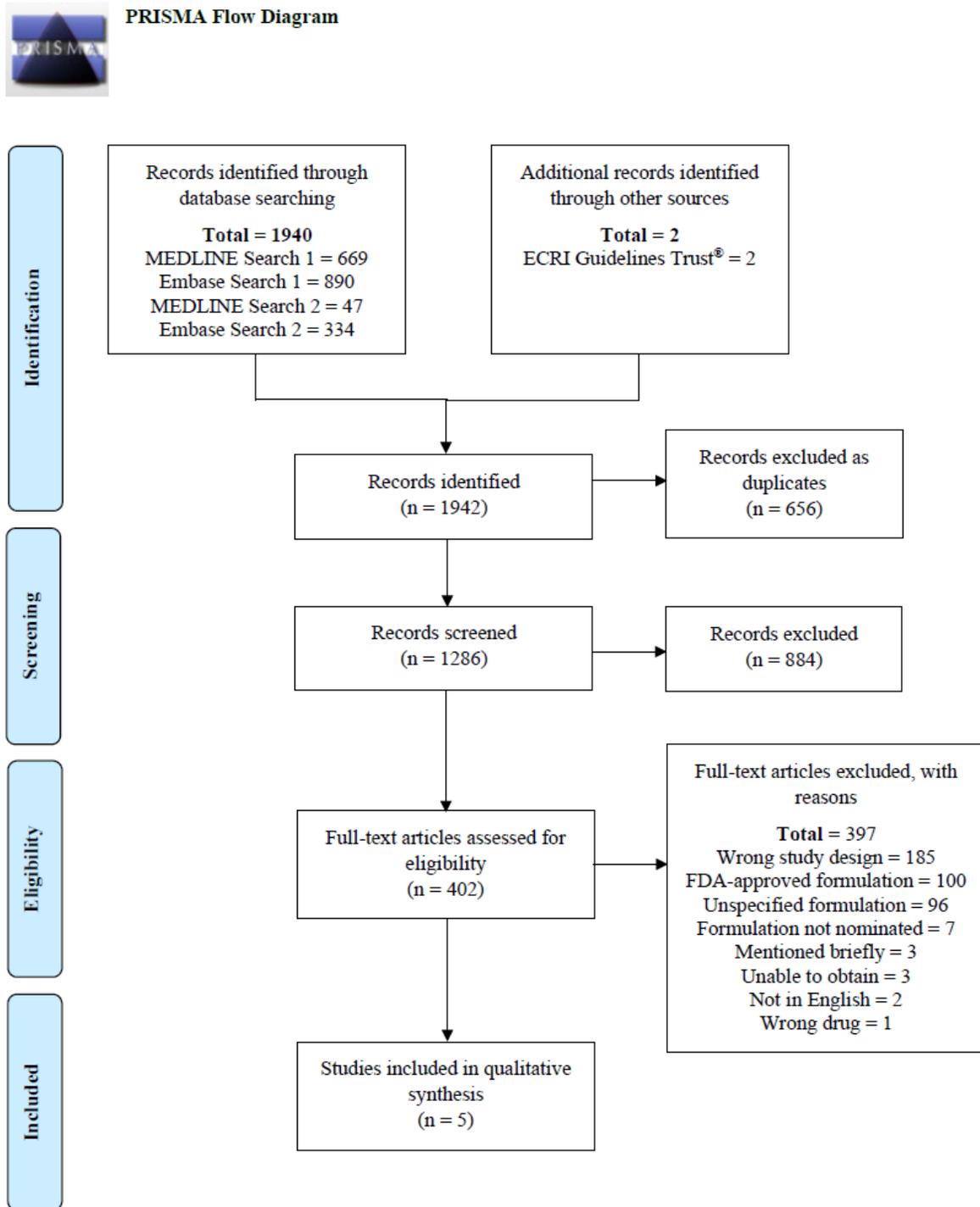
Mupirocin resistance increases with extended or repeated use of the drug, although this relationship has not been consistent in all studies.^{49,74} A 2010 case-control study, conducted at a Veterans Affairs Medical Center in Providence, Rhode Island, found 3 independent risk factors for mupirocin-resistant MRSA: exposure to mupirocin in the year prior to the resistant culture-related admission; treatment with cefepime in the prior year; and *Pseudomonas aeruginosa* infection in the prior year.⁷⁶ In a study published in 2015, investigators at Columbia University Medical Center in New York analyzed all *S. aureus*-positive skin cultures from the Division of Pediatric Dermatology over a 16-month period.⁷³ Three hundred fifty-eight isolates from 249 patients were evaluated; 35.3% of patients had a history of mupirocin use at the time of first culture. The most common primary dermatologic diagnoses were atopic dermatitis, dermatitis not otherwise specified, impetigo, folliculitis/pustulosis and abscess, and epidermolysis bullosa. The overall prevalence of mupirocin resistance was 31.3%, with high-level resistance detected in the majority of isolates (96 of 112, 85.7%). The only significant risk factor for mupirocin resistance in per-isolate, initial isolate, and ever-resistant analyses was history of mupirocin use. Conversion to mupirocin resistance in the absence of mupirocin administration was not documented. The authors suggested that “Judicious clinical use of mupirocin, particularly in high-risk populations, may prevent the development of additional and widespread resistance.”⁷³

The prevalence of mupirocin resistance varies considerably by geographic region and/or patient population.^{77,78} In 2014, Biedenbach et al. investigated the susceptibility of *S. aureus* isolates cultured from patients with SSTIs at 6 dermatology clinics in 5 states: Alabama, Arkansas, California, Florida and Texas.⁷⁸ The overall rate of MRSA from 218 isolates was 29.4%. The overall rate of mupirocin resistance among these isolates was 10.6% (23/218), with high- and low-level resistance in 8.7% (19/218) and 1.8% (4/218) of the isolates, respectively. The rate of mupirocin resistance differed among the states, with Florida having the highest rate of mupirocin resistance at 8.3% (18/218, or 25% of the 71 isolates from that state). Khoshnood et al. summarized resistance rates published in 43 studies from 23 countries between 1992 and 2017.⁷⁵ Rates of high-level mupirocin resistance ranged from 0.5% (study from US, published in 2009) to 98% (study from Greece, published in 2017). Rates of low-level mupirocin ranged from 0% (study from South Korea, published in 2003) to 46.7% (study from India, published in 2014). A 2020 systematic review and meta-analysis investigated the prevalence of mupirocin-resistant *S. aureus*, mupirocin-resistant MRSA, high-level mupirocin-resistant *S. aureus*, and high-level mupirocin-resistant MRSA finding pooled and average prevalence of 7.6% (95% confidence interval 6.2%–9.0%), 13.8% (12.0%–15.6%), 8.5% (6.3%–10.7%) and 8.1% (6.8%–9.4%), respectively.⁷⁷ The highest pooled prevalence of mupirocin-resistant *S. aureus* was found in the Americas. A trend of increasing prevalence of mupirocin-resistant *S. aureus* from 2011 to 2015 was detected. The authors posited that an explanation for this observed increase in resistance is an increasing trend in overall *S. aureus* infections and shift in antibiotic pressures.⁷⁷ The authors concluded that “The findings support the notion that routine diagnostic testing, identification

of carriers, national and organisational guidelines for infection control, surveillance and antibiotic stewardship measures, education and mupirocin prophylaxis are extremely important in the successful reduction of resistance to mupirocin, especially in MRSA isolates.”⁷⁷

In a 2009 review on nasal decolonization of *S aureus* with mupirocin, the authors concluded that “The rising emergence of *S. aureus* resistance to mupirocin will eventually reach a point at which its benefits are restricted to the extent that its use is no longer economically viable.”⁴⁹ However, studies have shown that restricting mupirocin use can reduce resistance in settings with a high rate of resistance.⁷⁴ In 2005, Vivoni et al. described their experience at a hospital in Brazil where from 1990 to 1995, nasal and/or topical mupirocin were administered (3 times a day for 5 days) to all patients either colonized or infected with MRSA.⁷⁹ In 1995, 65% (28/43) of MRSA isolated from patients showed mupirocin resistance; 44% (19/43) of the MRSA isolates demonstrated high-level resistance. Due to concern about widespread mupirocin resistance, use of the drug was restricted to nasal decolonization in patients with no clinical signs of *S aureus* infection and no skin lesions. *S aureus* isolates cultured from patients after implementation of these restrictions had a mupirocin resistance rate of 15%. The authors concluded that “The emergence and spread of mupirocin resistance and the imminent loss of this drug as an important agent in the control of MRSA emphasize the importance of using it judiciously.”⁷⁹ Walker et al. demonstrated the decline of mupirocin resistance at a Veterans Affairs Medical Center in Tennessee after first introducing recommendations for judicious use of mupirocin, and then administrative control of mupirocin prescriptions.⁸⁰ As the number of mupirocin prescriptions per 1000 patient days declined from a high of 3 (400 prescriptions per year) to a low of 0.1 (9 prescriptions per year), so too did the rate of high- and low-level mupirocin-resistant *S aureus* isolates decline from 31% to 4% and 26% to 10%, respectively.

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: <http://www.prisma-statement.org/>.

Table 3. Types of studies

| Types of Studies | Number of Studies |
|-------------------------------|-------------------|
| Descriptive ¹⁸⁻²⁰ | 3 |
| Observational | 0 |
| Experimental ^{16,17} | 2 |
| Clinical practice guideline | 0 |

Table 4. Number of studies by country

| Country | Number of Studies |
|--|-------------------|
| Australia ¹⁶ | 1 |
| United States (US) ¹⁸⁻²⁰ | 3 |
| Multiple Countries <ul style="list-style-type: none"> • Malaysia, US¹⁷ | 1 |
| Total US ^a : 4 Total Non-US Countries ^a : 2 | |

^aStudy 80 counted in both US and non-US total.

Table 5. Summary of included studies

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (No. of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|--|--|--|---|---|
| Indication 1: <i>Staphylococcus aureus</i>-associated chronic rhinosinusitis | | | | | |
| Jervis-Bardy et al., 2012, Australia ¹⁶ | Double-blind, randomized, placebo-controlled | 25 Patients with <i>Staphylococcus aureus</i> (<i>S. aureus</i>)-positive chronic rhinosinusitis (CRS) recalcitrant to surgery <ul style="list-style-type: none"> • Mupirocin rinses (55.5%, median 59 y, interquartile range 47-71 y) • Saline rinses (65.3%, median 55 y, interquartile range 41-64 y) | <ul style="list-style-type: none"> • Mupirocin nasal rinse + oral dextrose tablets (11) • Saline nasal rinse + oral amoxicillin / clavulanic acid tablets (14) | Pre- and posttreatment questionnaire, which included Sino-Nasal Outcome Test-20 (SNOT-20) and sinus visual analog symptom (VAS) score; culture swab; scoring of digital recording of nasal cavity | “Mupirocin nasal rinses are an effective short-term anti- <i>S. aureus</i> treatment in surgically recalcitrant CRS as assessed by microbiological and selected clinical criteria.” |
| Shikani et al., 2018, US ¹⁸ | Prospective | 16 Patients with methicillin-resistant <i>S. aureus</i> (MRSA)-associated recalcitrant chronic rhinosinusitis (41%, mean 44 y) | Intranasal installation of hydroxyl-ethylcellulose gel that released culture-directed antibiotic and mometasone. Starting 48 hours after gel placement, nasal saline rinses, and nebulization with same antibiotic and mometasone. Culture-directed antibiotics: <ul style="list-style-type: none"> • Mupirocin (5) • Tobramycin (1) • Vancomycin (10) | Lund-Kennedy symptoms, endoscopic appearance, microbial burden | “Our findings demonstrate that topical therapy is an effective method for treating MRSA-associated refractory CRS.” |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (No. of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|-----------------------------|--|---|---|--|
| Solares et al., 2006, US ¹⁹ | – | 24 Patients with MRSA-exacerbations of chronic rhinosinusitis (37.5%, mean 61 y, range 38-82 y) | 42 MRSA-positive cultures from 24 patients treated with: <ul style="list-style-type: none"> • Mupirocin nasal irrigation + oral doxycycline (24 episodes) • Mupirocin nasal irrigation + oral trimethoprim-sulfamethoxazole (4) • Mupirocin nasal irrigation alone (7) | Symptoms, endoscopy, and bacteriology | “Mupirocin nasal irrigations may avoid the need for intravenous antibiotics, which often provide temporary benefits and entail greater cost and morbidity. Thus, mupirocin nasal irrigations may provide a relatively simple means for the management of MRSA exacerbations of CRS.” |
| Indication 2: Postoperative endoscopic endonasal surgery | | | | | |
| Ng et al., 2019, Malaysia, US ¹⁷ | Randomized controlled trial | 20 Patients who had undergone endoscopic endonasal surgery for skull base lesions (45%, range 19-73 y) | <ul style="list-style-type: none"> • Mupirocin nasal lavage (10) • Alkaline nasal lavage (control, 10) | Sino-Nasal Outcome Test-22 (SNOT-22) questionnaire, nasal endoscopy score | “This study, with a level of evidence of 1B, suggests that, in patients undergoing endoscopic skull base surgery, mupirocin nasal lavage use improves outcomes in terms of sinonasal morbidity.” |
| Indication 3: Empty nose syndrome | | | | | |
| Nsouli et al., 2017, US ²⁰ | Case report | 34-Year-old female and 28-year-old male with signs of empty nose syndrome postnasal turbinectomy | Mupirocin nasal saline solution, flunisolide aqueous nasal spray, environmental control | Improvement in symptoms, nasal inspiratory peak flow rate | “The management of patients with ENS [empty nose syndrome] requires collaborative teamwork between otolaryngologists and allergists and could be achieved by an initial allergy evaluation and treatment and, ultimately prevented with a careful turbinate-sparing technique.” |

Abbreviations: –, not provided; *Staphylococcus aureus*, *S aureus*; CRS, chronic rhinosinusitis; MRSA; methicillin-resistant *Staphylococcus aureus*; SNOT-22, Sino-Nasal Outcome Test-22.

^aAs defined by authors.

Table 6. Dosage by indication – US

| Indication | Dosage | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|--|---------------------------------------|---------------|-------------|-------------------------|-----------------------|
| <i>Staphylococcus aureus</i> -associated chronic rhinosinusitis ^{18,19} | 5 mL/nares, once a week | 1 mg/mL | Gel | Nasal | 6 weeks |
| | 22 mg, twice a day | 440 mg/L | Solution | | 4-6 weeks |
| | 5 mg | – | – | Nebulized | 6 weeks |
| Post-operative endoscopic endonasal surgery ¹⁷ | Dose not mentioned, three times a day | – | Lavage | Nasal | 28 days |
| Empty nose syndrome ²⁰ | – | 0.05% | Solution | Nasal | – |

Abbreviations: –, not provided.

Table 7. Dosage by indication – non-US countries

| Indication | Dosage | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---------------------|---------------|-------------|-------------------------|-----------------------|
| <i>Staphylococcus aureus</i> -associated chronic rhinosinusitis ¹⁶ | 240 mL, twice a day | 125 mg/240 mL | Rinse | Nasal | 28 days |

Abbreviations: –, not provided.

Table 8. Number of studies by combination

| | Combination Formula | Number of Studies |
|----------------------------|--|--------------------------|
| Nominated | Mupirocin 2% / Betamethasone dipropionate 0.05% – cream | 0 |
| | Mupirocin 2% / Hyaluronic acid sodium salt 0.5% / Niacinamide 4% – cream | 0 |
| | Mupirocin 2% / Metronidazole 1% / Tranilast 1% – ointment | 0 |
| | Mupirocin 2% / Aloe vera 0.2% / Lidocaine 2% / Tranilast 1% – ointment | 0 |
| | Mupirocin 2% / Aloe vera 0.2% / Metronidazole 1% / Tranilast 1% – ointment | 0 |
| | Mupirocin 2% / Levocetirizine dihydrochloride 2% / Tranilast 1% / Triamcinolone acetonide 0.025% – cream | 0 |
| | Mupirocin 2% / Clobetasol propionate 0.05% / Ibuprofen 2% / Salicylic acid 5% / Urea 20% – cream | 0 |
| Others found in literature | Mupirocin 1 mg/mL / Mometasone 240 mcg/mL – nasal gel ¹⁸ | 1 |
| | Mupirocin 5 mg / Mometasone 0.6 mg – not provided ¹⁸ | 1 |

Table 9. Compounded products – US

| Indication | Publication Year | Compounding Method | Dosage Form | Final Strength |
|---|-------------------------|--|--------------------|-----------------------|
| <i>Staphylococcus aureus</i> -associated chronic rhinosinusitis ¹⁸ | 2018 | Hydroxyl-ethylcellulose gel specially prepared by local compounding pharmacy to release culture-directed antibiotic and mometasone | Gel | 1 mg/mL |

Abbreviations: –, not provided.

Table 10. Compounded products – non-US countries

| Indication | Compounding Method | Dosage Form | Final Strength |
|---|--|-------------|----------------|
| <i>Staphylococcus aureus</i> -associated chronic rhinosinusitis ¹⁶ | Mupirocin 125 mg + proprietary buffered salts blend, dissolved in 240 mL boiling water | Solution | 125 mg/240 mL |

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Six SMEs discussed mupirocin. Among these 6 SMEs, there were 3 doctors of podiatric medicine, 2 medical doctors, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in allergy, dermatology, infectious disease, and wound care and worked in academic medical centers, a hospital setting and private practice. The SMEs had been in practice for 1 to 40 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Mupirocin was nominated alone and in combination with other APIs as a topical gel, cream, ointment, solution, or suspension for use in the management of superficial skin infections, nasal infections and wound healing. Mupirocin was also nominated for use as a nasal spray. All of the SMEs who were interviewed were familiar with mupirocin. An SME specializing in dermatology used topical mupirocin for the treatment of superficial *Staphylococcus* infections in patients with atopic dermatitis or psoriasis. This SME suggested that sometimes in these patients it is a “a fine line” between whether they are treating an actual infection or just clearing bacterial colonization. The SME remarked, “There is some literature, actually, some pretty good literature to show that the skin microbiome in atopic dermatitis is disturbed by overcolonization of staph. And that that can further drive atopic dermatitis. And so there does seem to be some good reason to treat the staph colonization.” The SME continued:

One really classic example is in some people with eczema; they'll get these sorts of fissures around their ears, their ear lobes that will look eczematous, but also have this yellowishness. And that's actually a really good sign of staph infection. And so it makes a lot of sense to treat with some topical antibiotics for that. So, I guess it's hard to call it exactly infection because it's not what we typically think of as like overgrowth of sort of invasive pathogen really driving the entire process. But at the same time, it's not sort of just benign colonization because they are contributing to the disease progression.

Another SME, who specialized in podiatry, used mupirocin for superficial skin and soft tissue infections of the foot as well as nail infections. This SME preferred to use mupirocin ointment for these infections. A second SME who specialized in podiatry also used mupirocin; this SME used the drug in patients who had undergone surgical procedures, particularly patients with diabetes, because it was effective against MRSA. Mupirocin was applied along with a protective dressing postoperatively. A third SME who specialized in podiatry had also used mupirocin. This SME commented:

Mupirocin is unlike some of these other drugs that you might talk about. There's actually literature to support mupirocin. I mean, it had an indication; it still has an indication. I think it was a fairly limited like impetigo and primary pyoderma, something along those lines there. If you can explain to me what primary pyoderma is, be my guest, but there had been some literature, at least in the impetigo world, from mupirocin. It was very effective and very effective against gram positives. So, it's good against staph and strep.

This SME was not aware of any literature on the use of mupirocin in the management of infection or colonization in patients with diabetic foot or venous leg ulcers and was unsure how effective antibiotics were when applied topically to wounds. This SME noted that there was some evidence to support the use of topical antimicrobial solutions or washes in wound management and mentioned the emergence of wound dressings that, “...have some antimicrobial activity. They have all of the wound growth factors built in... That again, people talk about having some antimicrobial activity just because of the way they

interact with the surface of the wound, as opposed to slathering on mupirocin or something along those lines.”

Three SMEs had used topical mupirocin in the management of wounds. An SME specializing in podiatry used mupirocin ointment and collagenase, an enzyme that breaks down necrotic tissue, for wounds on the foot. This SME typically dispensed these products to the patient for application at home with the assistance of a nurse or home health aide. One SME who specialized in wound care used a variety of topical products in their practice, including antimicrobial solutions to clean wounds and saturate gauze dressings to pack in a wound, impregnated dressings and occasionally, topical ointments. Ointments were the preferred topical form in wounds with drainage because they remained in place better than other forms. The use of topical products other than antimicrobial solutions, saline and dressings was usually limited to patients with superficial (including full thickness) wounds. This SME did not use a lot of topical antibiotics because they were concerned about the development of antibiotic resistance; if a patient required antibiotics for treatment of an infection, then they were administered systemically. An SME who specialized in podiatry had a similar opinion, stating, “You need to, if you've got drainage and then you've got to take a culture, you've got to identify what the organism is, and then you've got to treat that appropriately and the best way to approach it is going to be a systemic antibiotic.” The SME who specialized in wound care noted that if they had a patient with poor circulation, then they might apply a topical antibiotic along with prescribing systemic antibiotics. This SME had used mupirocin, remarking:

Oh, yes. We used it. Especially when it first came out, we used it a lot. Then we found out it's beginning to have resistance to it; so it's not quite as effective as it used to be. But, yes, it's very commonly used since we know that Neosporin® [bacitracin / polymyxin B / petrolatum] as a topical has a lot of allergens to it; so we go with Polysporin but then if it's something that we're not really getting good coverage there or we're worried about MRSA from the community, then we will use it on small wounds. It's not something that I would use on big wounds or extensively. It would be a small group of patients that you would use that on.

This SME indicated that they do try to culture wounds prior to initiating antibiotic therapy, but it is not always possible to do so and therefore they do “a fair amount of empirical treatment.” The SME, who worked primarily with oncology patients, commented that in this patient population, it is easy to assume that a small local wound originated due to MRSA because they often see patients with community-acquired MRSA. This SME avoided products with allergenic ingredients because a reaction to an ingredient would be particularly concerning in patients undergoing treatment for cancer. This SME commented:

You really don't want to get things that they're either going to be allergic to or have any kind of reaction because they are in the middle of treatment. I was talking even about in our wound care clinic, we didn't tend to use any kind of compounded solutions like that. Plastics used it. They also shared our clinic space in the wound clinic. That was just not our practice to mix things up a lot.

This SME went on to say that they had worked in a clinic affiliated with a dermatology practice, so they followed many dermatologic standards of care in managing patients with wounds, including limiting additives, fragrances and other ingredients that might provoke an allergic reaction. This helped the SME make decisions about product use, “really looking to dermatology to say, ‘Is this good practice for skin in general?’ And then when you've got broken skin and you're putting something on it, you have to think about absorption and reaction possibilities as well for every product you use.” An SME who specialized in podiatry mentioned that “the problem with mupirocin is that there's a preservative within the vehicle typically, or I should say the brand name, Bactroban®, that could cause an allergic reaction. So that's why

there was an alternative mupirocin that came out that was lacking that preservative. So, it's more the formulation than it is the drug.” This SME said that they were able to get a generic mupirocin formulation without the preservative but with a generic product “you don’t know what you’re getting.”

The SME who specialized in wound care also had experience working with patients with ostomies. This SME stated that they did not typically use topical products for antimicrobial prophylaxis around ostomy sites. The SME commented:

No, we don't usually use that prophylactically at all. We really don't do prophylactic, any kind of antimicrobial. The product that we use on skin sometimes is a copolymer kind of coating action. It's in the family with the surgical glue, that it's a really less potent kind of, that type of thing. That's what we usually use for protection or preventing problems, but a lot of the ostomy products now have advanced so much that when they come to market with any kind of revisions, they're tested just being applied to clean dry skin around the stoma and usually that is successful, and we don't have to add a lot of things there.

This SME observed that some ostomy products are now impregnated with skin moisturizers, such as ceramides and Manuka honey, to protect the skin around the ostomy site and prevent the development of dermatitis.

Three SMEs had concerns about the development of resistance with the use of topical antibiotics while one SME did not. The SME who specialized in dermatology commented:

You know, I think dermatology is one of the biggest offenders in terms of overusing antibiotics. We use it for a lot of things, rosacea, acne. A lot of surgeons use it, sort of outside evidence-based guidelines, for them to sort of lower their infection rates even though the evidence is that it doesn't necessarily lower infection rates. And so yeah, I do. I do worry about that. I think you're right, that it might be prudent to take antibiotics out of mixes and make sure that they are prescribed separately to make sure that they're actually being intended in a situation where they're needed rather than just being sort of added on without any particular need. Yeah. I think that does make sense.

As mentioned earlier, the SME specializing in wound care did not use a lot of topical antibiotics because they were concerned about the development of resistance. An SME specializing in podiatry was aware that mupirocin resistance had emerged as a result of its use for MRSA decolonization of the anterior nares. Another SME specializing in podiatry had not encountered resistance to mupirocin despite using it frequently for their patients.

Mupirocin was nominated for use in combination with the following APIs: aloe vera, betamethasone dipropionate, clobetasol, hyaluronic acid, ibuprofen, levocetirizine, lidocaine, metronidazole, niacinamide, tranilast, triamcinolone acetonide, salicylic acid and urea. As part of Phase 3, one of the nominators provided additional information regarding the multi-ingredient products contained within the mupirocin nomination. The nominator stated that the combinations would be used to treat superficial skin infections and fungating wounds. The nominator indicated that these topical dosage formulations were necessary because they do not contain harmful excipients found in FDA-approved products and these combinations of active and inactive ingredients cannot be found in any commercially available formulations. The nominator identified several inactive ingredients as potentially harmful allergens or irritants, including: ethanol, isopropyl palmitate, lactic acid, laureth-7, oleyl alcohol, methylparaben, mineral oil, polyethylene glycol, propylene glycol, silicon dioxide, sodium hydroxide, trolamine and white petrolatum. According to the nominator, mupirocin and metronidazole were included in these combinations for their antibacterial properties; tranilast was included for its anti-allergy and anti-

inflammatory properties; triamcinolone was also included for its anti-inflammatory properties; lidocaine was included in one combination for its anesthetic properties; and levocetirizine was included in one combination for its anti-itch properties.

Two SMEs commented on the combination of mupirocin, levocetirizine, tranilast and triamcinolone acetonide. Upon being presented with this combination, an SME who specialized in allergic conditions remarked:

I don't even know what that last one is. I mean, I guess they're trying to use that for eczema, I would assume, because we do have a lot of eczema patients, because we have patients who also have topical, staph infections. So usually we'll say, 'Okay, here's triamcinolone for when your flares. And then here's mupirocin for these areas that are open and crusty, and things like that.' So that's kind of an interesting one right there. That's interesting that they could even do Xyzal[®] [levocetirizine] all topically, but that'd be interesting.

This SME concluded, "I just thought it was interesting that there were so many things they were thinking. I don't think I have that much of imagination. I would never have thought of it." The SME who specialized in dermatology was similarly puzzled with this combination, in particular the proposed topical use of levocetirizine. This SME observed:

So, it's antihistamine. I think, probably what they're going after is, is sort of mast cell-induced itch, and so I can imagine this being used for something like urticaria or something like that. But on the other hand, you're right. I don't know that it's going to be super effective as a topical, and we very regularly give systemic oral antihistamines for those kinds of things anyway. And I guess, we give it for probably pretty much anything that this would be used for. So, the combination, and it's hard for me to say what the intended use of this is, but the combination with mupirocin, it brings up a question in my mind whether this was intended for atopic dermatitis and in that case too, we'll give systemic antihistamines if that's an issue as well. So, I'm not sure that there's a lot of benefit to having that as a topical. Yeah. I don't think there would be.

This SME also commented on the combinations of mupirocin, hyaluronic acid and niacinamide and mupirocin, clobetasol, ibuprofen, salicylic acid and urea. According to this SME, hyaluronic is typically used in dermatology for injectable fillers; it has been used topically to help increase the turgidity of the skin, but the SME questioned its use as an active ingredient. When asked about the use of mupirocin in combination with hyaluronic acid and niacinamide, the SME responded, "Again, it's hard for me to say what exactly they're hoping to get out of that. I don't know. I think you'd need to really ask what the intent is. I'm having a hard time sort of imagining exactly what it would be, but it's possible there's something that it's being active for." Upon further reflection, the SME postulated that this combination might be used after laser treatments where the mupirocin would prevent *Staphylococcus* infection, the hyaluronic acid would increase water retention in the skin and the niacinamide would brighten the skin. If this combination were to be used as a prophylactic therapy after laser treatment, then the SME thought that it would be useful to have it in the office to apply immediately after the treatment. The SME theorized that the combination of mupirocin, clobetasol, ibuprofen, salicylic acid and urea could be used in conditions associated with hyperkeratosis, such as psoriatic plaques, because the salicylic acid and urea were keratolytic agents, the clobetasol would treat the inflammatory process of psoriasis, and the mupirocin would control *Staphylococcus* colonization associated with the hyperkeratotic areas. The SME could not surmise why ibuprofen was included in this combination.

Three SMEs expressed concerns about the lack of evidence for the efficacy of compounded combination products. A SME who specialized in podiatry commented on the use of compounded combination

products, saying, "...a lot of doctors do use them. But I do not." This SME had concerns about the miscibility of the compounds in these products and overall stability of the products once packaged. If necessary, this SME had patients apply multiple topical products "separately at different times of the day." The SME who specialized in wound care said, "We don't send anything to a compounding pharmacy or really have any special concoctions made," continuing:

We don't do a lot of our own compounding because we feel like there's not a lot of evidence for some of the combinations that we see others using or have reported when we see patients that are managed in other clinics because we weren't real comfortable with combining things that don't have at least a little science behind, 'this doesn't inactivate that, and these two can play together and not cause a really bad reaction of some sort.'

This SME had worked in a practice that shared clinic space with plastic surgery and noted that they used compounded products, including a combination product called 'DABS' that they used for wound care after plastic surgery. The SME thought that this product was a combination of antibiotics, one of which was possibly bacitracin. An SME specializing in podiatry used a commercially available combination ear drop, Cortisporin® (neomycin / polymyxin B / hydrocortisone), for postoperative care in patients who had undergone surgical nail procedures, typically for ingrown toenails. The SME favored this product because it provided antibiotics, to reduce infection, and an anti-inflammatory medication in an oily base, which "is good as a vehicle for that part of the body." The SME acknowledged that this product was not approved for this indication and suggested that the combination of an antimicrobial and steroid in a base appropriate for application to nails would be a desirable product.

Two SMEs observed that health care practitioners had different strategies for applying multiple topical products. One SME noted that some dermatologists recommend mixing multiple products together prior to application while others recommend applying the products in a layered manner, one after the other. The SME was of the opinion that the former method, mixing prior to application, was often easier for patients, stating, "I would say probably it doesn't matter because, I mean, for the most part, I suppose it's possible that something matters, but yeah, a lot of times, if it's intended to be applied at the same time and the excipients are consistent, then I'll say mix the two and put them on. Because that's usually easier for people to remember to do." Another SME, who specialized in wound care, shared that they used a commercially available enzymatic debriding agent, such as collagenase, at the base of a wound with a silver-impregnated dressing on top. This SME commented, "But a lot of clinicians do use a variety of compounds on top of that collagenase as a base. I don't know that you would ever physically mix it together, but you can apply one layer and then put something else on top of it." This SME also frequently used multiple topical products in patients who were incontinent:

We put them on individually so it's like a layered effect. Again, we're not going to mix it up in a cup and then smear it on somebody. We put on a little bit of this and that and the other. We do use a lot of the azole ointment, or creams first and then maybe the zinc oxide and the petrolatum stuff on top if incontinence and the fungus is really going strong.

This SME thought that a topical product with an antifungal drug and steroid would be a desirable combination, preferably in a form appropriate for application to an area prone to mechanical injury. This SME remarked, "As our population's heavier, there's more skin-to-skin contact so more yeasty stuff there or fungal stuff there. So yeah, a little bit of a steroid will calm that down as well so that combination would be a good combo." The SME observed that for at-home use, it would be easier to tell patients to apply a single topical combination product than layer multiple single-agent products.

Regarding the use of compounded products in their respective specialties, one SME who specialized in podiatry remarked:

Once upon a time, compounding was what you did in dermatology and medicine, because things weren't available. Then I think people again, did some really shady things and bad things. I've seen bad things over the years. So, I only use those compounding agencies when absolutely necessary. So, I end up prescribing a lot of things or some of the things that are already available over the counter.

Another SME who specialized in podiatry thought that use of compounded products within the specialty varied among practitioners. This SME observed:

I think there are podiatrists who are strictly doing traditional medications for the overall indications for which they've been approved. There are certainly people who are using compounded products. I have been to a number of lectures and meetings. They tend to be not true continuing education meetings, but rather lunch-and-learn meetings, promotional meetings, where compounding pharmacies have spoken to podiatrists. And in some of them, the podiatrist is actually speaking to other podiatrists, and they have all their preprinted prescription forms off with this pain treatment and this antifungal treatment and this antibiotic treatment.

The SME specializing in wound care often dispensed dressing materials to patients requiring frequent bandage changes at home and then ordered additional products from a distributor to be delivered to the patients' homes for ongoing care. This SME used commercially available products prepared in a manufacturing situation and marketed for wound care, such as Dakin solution (dilute sodium hypochlorite), Vashe[®] Wound Solution (hypochlorous acid), PolyMem[®] dressings and silver-impregnated dressings. This SME noted that home health nurses were sometimes involved with patient care, and their companies may provide supplies, but these were also commercially prepared products.

As part of Phase 3, one nominator provided additional information regarding the multi-ingredient products contained within the metronidazole nomination.

Mupirocin 2% / niacinamide 4% will be compounded as a topical cream to treat superficial skin infections applied multiple times throughout the day for multiple days. This product is used by practitioners as a nonpatient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: polyethylene glycol and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include classified as expected to be toxic or harmful, human immune and respiratory toxicant or allergen, human endocrine disruptor, classified as skin irritant. Mupirocin is added for its antibacterial properties and lidocaine for its anesthetic properties; the reason niacinamide is added to the formulation is not specified. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Mupirocin 2% / metronidazole 1% / tranilast 1% will be compounded as a topical ointment to treat fungating wounds applied multiple times throughout the day for multiple days. This product is used by practitioners as a nonpatient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, polyethylene glycol, sodium hydroxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants, their hazardous concerns include classified as expected to be toxic or harmful, found to cause seizures and severe

neurological symptoms, possible human carcinogen, violation of industry recommendations – restricted in cosmetics; use, concentration, or manufacturing restrictions – not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, classified as skin irritant. Mupirocin is added for its antibacterial properties, metronidazole for its antibacterial properties, and tranilast for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Mupirocin 2% / betamethasone dipropionate 0.05%, mupirocin 5% / clobetasol propionate 0.05% / ibuprofen 2% / salicylic acid 5% / urea 20%, and mupirocin 2% / levocetirizine dihydrochloride 2% / tranilast 1% / triamcinolone acetonide 0.025% will not be compounded as these formulations have been discontinued.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 16 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 16-19 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of

concentrations or sizes available. One participant commented that “at baseline, already, we manipulate about 80% of what we dispense to patients” and another stated that “there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids.” One participant stated that “we’re trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible.” Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that “we absolutely buy as many pressor drips as we can.” One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that “they would prefer to have a syringe form.”

Another theme regarding deciding what products to purchase from an outsourcing facility focused on the use and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product use and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that “we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out.” Another participant, while they do not obtain a lot of products from outsourcing facilities, stated that “when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals with one participant stating that “it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital” and another who pointed out that “without 503B, we would've been in significant trouble.” One participant commented that “even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when.” Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating “it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing.”

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, “we obviously need to provide product with much extensive beyond-use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “we might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in operating rooms and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list.” The participant continued that “similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘no, we can't have it, and that's too big! It won't fit!’ We want it in this format, and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500-mL bag, but the clinical guideline is a 150-mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL].” The participant pointed out that “it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose; is it a unit dose or isn't it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can't accept the additional volume if it's a true shortage. If you're not with them preshortage, you're not going to get products when you need it during the shortage.” The participant added that “typically in a shortage, you learn to live without them. You have to.” Additionally, if the shortage is due to a scarce API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on APIs. If sterile becomes short, they quickly switch to producing through APIs, which ASHP [American

Society of Hospital Pharmacists] and the FDA allows.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

A few participants commented on the use of APIs by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using APIs if there is a shortage, stating, “I think the FDA has really looked closely at APIs, and they're slowly pushing the 503B outsourcers to a sterile to sterile.” Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population.” However, another participant from a children’s hospital stated that the need for a preservative-free option was never the reason they obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because “they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there.” Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant also noted that while the evidence does not support many of the ingredients used in topical pain products, “there are select patients. It's very rare that taking that cream away from them actually causes more harm than good.” A few participants commented that there is a gap in the market for nonsterile products with one stating, “I think that there is a large opportunity for more nonsterile products to be produced by 503Bs.” Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding

obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated, “there's not many 503Bs doing the nonsterile for clinic use.” As a result, the inpatient pharmacy is often asked to take on this role, but “you don't have the space or the staff to do that.”

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical; we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility.” The participants commented that alum is only needed a few times a year. However, as one participant observed, “when you need it, it's an emergency” and another noting that it “is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis.” As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, ‘this is an old, really old. I don't even know why we're using it’ and basically approved for us to not even make it anymore for now.”

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility: 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into “a very specific kind of pump that's used to deliver a very specific kind of chemotherapy.” When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin “it can go three months or something like that, so it's a huge patient satisfier to have that concentration available.” The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that “our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is only available as a 500-mL bag, and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that “it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to the “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of FDA quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo behold they're shut down, or closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.” Another challenge was related to outsourcing facilities using APIs to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that “they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs [that] they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways.”

Results of survey

Thirty-three people responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 9 (14% of 64 responses, where respondents were allowed to select multiple products) used mupirocin as a compounded topical product (refer to Table 12). Fourteen (100% of 14

responses) respondents reported using compounded topical products in combination with other active pharmaceutical ingredients as a multi-ingredient product.

Ten respondents (50% of 20 responses, where respondents were allowed to select multiple reasons) reported using compounded topical products due to lack of commercial products in an appropriate dosage form, strength or combination, patient allergies preventing use of commercially available products (1, 5%), other patient conditions preventing use of commercial products (3, 15%), or no commercially available products (3, 15%). Three respondents (15%) used compounded topical products because ‘oral medications are contraindicated due to comorbidities,’ ‘very good for medication use, patient compliance is improved with need to apply medication,’ and ‘decreased systemic effects and higher concentrations at specific areas of need.’ Refer to Table 13 for reasons for using compounded topical products.

The majority of respondents (11 of 13 responses, 85%) did not stock non-patient-specific compounded products at their practice. Respondents reported obtaining compounded topical products by purchasing, or having the patient purchase the product from a compounding pharmacy (12 of 14 responses, where respondents were allowed to select multiple avenues, 86%) or outsourcing facility (2, 14%). Refer to Table 15 for how respondents obtained compounded products.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.4 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) used outsourcing facilities to obtain drug products, 4 (9%) did not use outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 17).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 18 for the categories of products obtained from outsourcing facilities.

One respondent (0.9% of 108 responses, where respondents were allowed to select multiple drug products) obtained mupirocin from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

| Terminal Clinical Degree | Responses, n (N = 29) |
|---|------------------------------|
| Doctor of Medicine (MD) | 0 |
| Doctor of Osteopathic Medicine (DO) | 0 |
| Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm) | 2 |
| Physician Assistant (PA) | 0 |

| | |
|--------------------------------------|--|
| Doctor of Podiatric Medicine (DPM) | 27 |
| No Response | 6 |
| Practice Setting | Responses, n (N = 35)^a |
| Physician office or private practice | 23 |
| Outpatient clinic | 6 |
| Hospital or health system | 3 |
| Academic medical center | 1 |
| Emergency room | 0 |
| Operating room | 2 |
| No response | 6 |

^aSome respondents reported more than one practice setting.

Table 12. Compounded topical products prescribed or administered

| Condition | Responses, n (N = 64)^a |
|-------------------|--|
| Clotrimazole | 15 |
| Fluconazole | 6 |
| Itraconazole | 9 |
| Ketoconazole | 11 |
| Metronidazole | 4 |
| Mupirocin | 9 |
| Zinc oxide | 3 |
| None of the above | 15 |
| No Response | 4 |

^aSurvey respondents allowed to select multiple products.

Table 13. Reasons for using compounded topical products

| Reason | Responses, n (N = 20)^{a,b} |
|---|--|
| Commercial product not available in desired dosage form, strength, or combination | 10 |
| Patient allergies prevent use of commercial products | 1 |
| Patient conditions prevent use of commercial products | 3 |
| No commercial products | 3 |
| Other ^b | 3 |

^aSurvey respondents allowed to select multiple reasons.

^bRespondents stated ‘oral medications are contraindicated due to comorbidities,’ ‘very good for medication use, patient compliance is improved with need to apply medication,’ and ‘decreased systemic effects and higher concentrations at specific areas of need.’

Table 14. Stock of non-patient-specific compounded topical products

| Do you stock non-patient-specific compounded topical products at your practice? | Responses, n (N = 13) |
|--|------------------------------|
| Yes | 2 |
| No | 11 |
| Not sure | 0 |
| No response | 20 |

Table 15. Obtainment of compounded topical products

| How do you obtain compounded topical products? | Responses, n (N = 14)^a |
|---|--|
| Compound yourself at practice | 0 |
| Product compounded by in-house pharmacy | 0 |
| Purchase from compounding pharmacy | 12 |
| Purchase from outsourcing facility | 2 |
| No response | 21 |

^aSurvey respondents allowed to select methods.

Table 16. Demographics of prequestionnaire respondents' facilities

| Type of Facility | Responses, n (N = 102) ^a |
|---------------------------------|-------------------------------------|
| Academic medical center | 15 |
| Acute care hospital | 16 |
| Children's hospital | 8 |
| Community hospital | 11 |
| Critical access hospital | 2 |
| Dialysis center | 2 |
| Federal government hospital | 4 |
| Health system | 15 |
| Inpatient rehabilitation center | 4 |
| Long-term acute care hospital | 3 |
| Outpatient surgery center | 6 |
| Rural hospital | 2 |
| Skilled nursing facility | 0 |
| Specialty hospital ^b | 4 |
| Trauma center | 5 |
| Urban hospital | 5 |
| Number of Beds | Responses, n (N = 39) |
| < 50 | 4 |
| 50-99 | 3 |
| 100-199 | 1 |
| 200-299 | 4 |
| 300-399 | 5 |
| 400-599 | 3 |
| > 600 | 19 |

^aRespondents allowed to select more than one type of facility.

^bSpecialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

| Categories | Responses, n (N = 143)^a |
|---|---|
| Backorders | 20 |
| Convenience | 19 |
| Cost | 10 |
| Need for concentrations not commercially available | 19 |
| Need for multi-ingredient products not commercially available | 10 |
| Need for preservative-free products | 3 |
| Need for ready-to-use products | 27 |
| No FDA-approved product available | 7 |
| No onsite compounding facility | 1 |
| Onsite compounding facility not equipped to compound all necessary products | 19 |
| Other ^b | 8 |

^aRespondents allowed to select multiple categories.

^bRespondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for using outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

| Categories | Responses, n (N = 142)^a |
|--|---|
| Cardioplegic solutions | 14 |
| Dermatologic preparations | 6 |
| Dialysate solutions | 0 |
| Fluids | 8 |
| Ophthalmic preparations | 10 |
| Patient-controlled analgesia | 20 |
| Ready-to-use anesthesia syringes | 25 |
| Ready-to-use antibiotic syringes and/or bags | 14 |

| | |
|--------------------------------------|----|
| Ready-to-use electrolyte solutions | 5 |
| Ready-to-use vasopressor solutions | 18 |
| Total parenteral nutrition solutions | 16 |
| Other ^b | 6 |

^aRespondents allowed to select multiple categories.

^bRespondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 19. Products obtained from an outsourcing facility

| Product | Responses, n (N = 108)^a |
|--------------------------------|---|
| Acetylcysteine | 1 |
| Adenosine | 2 |
| Aluminum potassium sulfate | 2 |
| Aspartic acid | 0 |
| Atenolol | 0 |
| Atropine | 9 |
| Baclofen | 4 |
| Betamethasone | 0 |
| Biotin | 0 |
| Bupivacaine | 8 |
| Calcium chloride | 1 |
| Caffeine sodium benzoate | 0 |
| Cholecalciferol | 1 |
| Chromium chloride | 0 |
| Clonidine | 0 |
| Dexamethasone sodium phosphate | 0 |
| Diclofenac | 0 |
| Gentamicin | 0 |

| | |
|-------------------------|----|
| Glycerin | 1 |
| Hydroxyzine | 0 |
| Ketamine | 14 |
| Levocarnitine | 0 |
| Lidocaine | 8 |
| Lorazepam | 2 |
| Magnesium sulfate | 4 |
| Manganese chloride | 0 |
| Methylprednisolone | 0 |
| Midazolam | 15 |
| Mupirocin | 1 |
| Norepinephrine | 15 |
| Ondansetron | 0 |
| Phytonadione | 0 |
| Potassium chloride | 0 |
| Potassium phosphate | 0 |
| Prilocaine | 0 |
| Proline | 0 |
| Propranolol | 1 |
| Ropivacaine | 6 |
| Sodium chloride | 0 |
| Sodium citrate | 3 |
| Sodium phosphate | 0 |
| Tetracaine | 2 |
| Triamcinolone acetonide | 0 |
| Tropicamide | 0 |

| | |
|-------------------|---|
| None of the above | 8 |
|-------------------|---|

^aRespondents were allowed to select multiple products.

CONCLUSION

Mupirocin was nominated for inclusion on the 503B Bulks List as a topical cream, gel, ointment, solution or suspension, nasal spray, and otic preparation to treat skin and nasal infections. Mupirocin is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, the UK and the US. Mupirocin is available as an OTC product in Canada.

Six studies were included from the literature review. In 2 of the studies, mupirocin was administered as a nasal lavage solution for treating -associated chronic rhinosinusitis.^{16,19} In 1 study, mupirocin was administered as a nasal gel and via nebulization, both in combination with mometasone, for the treatment of *Staphylococcus aureus*-associated chronic rhinosinusitis.¹⁸ In 1 study, mupirocin was administered as a nasal lavage solution for management of sinonasal morbidity after endoscopic endonasal surgery.¹⁷ In 1 study, mupirocin was administered as a nasal solution for the treatment of empty nose syndrome.²⁰

Six SMEs discussed mupirocin, all of whom were familiar with the drug. The SMEs use mupirocin for the treatment of superficial bacterial infections of the skin, particularly in patients with atopic dermatitis or psoriasis, nail infections and postoperative care after surgical procedures of the foot. Two SMEs expressed a preference for mupirocin ointment. Two SMEs use mupirocin in the management of wounds. The SME who specialized in wound care indicated that the use of topical antibiotics was limited to small, superficial (including full thickness) wounds and systemic antibiotics were used to treat infected wounds, either alone or in conjunction with topical antibiotics. An SME who specialized in podiatry was not aware of any literature to support the use of topical mupirocin in the management of diabetic foot or venous leg ulcers; like the SME who specialized in wound care, this SME used systemic antibiotics for the treatment of infection. Three SMEs expressed concerns about the development of resistance with the use of topical antibiotics, including mupirocin, while one SME had not experienced resistance despite frequent use of topical mupirocin. None of the SMEs had used any of the proposed combinations and did not know of any evidence supporting the efficacy of these combinations. One SME specializing in podiatry expressed a desire for a combination product with an antibiotic and steroid for use in patients undergoing nail procedures. The SMEs acknowledged the use of compounded products within their specialties, but none of them used compounder products in their own practice.

As part of Phase 3, one nominator provided additional information regarding the multi-ingredient products contained within the metronidazole nomination. Mupirocin 2% / niacinamide 4% will be compounded as a topical cream to treat superficial skin infections and mupirocin 2% / metronidazole 1% / tranilast 1% will be compounded as a topical ointment to treat fungating wounds. Mupirocin is added for its antibacterial properties.

From the survey responses, 9 out of 33 respondents used compounded topical mupirocin. From the prequestionnaire, 1 respondent obtained mupirocin from a 503B outsourcing facility.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Method.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5:69.
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143.
6. Rist T, Parish LC, Capin LR, Sulica V, Bushnell WD, Cupo MA. A comparison of the efficacy and safety of mupirocin cream and cephalexin in the treatment of secondarily infected eczema. *Clin Exp Dermatol.* 2002;27(1):14-20.
7. Bork K, Brauers J, Kresken M. Efficacy and safety of 2% mupirocin ointment in the treatment of primary and secondary skin infections—an open multicentre trial. *Br J Clin Pract.* 1989;43(8):284-288.
8. Yankey H, Isaacson G. Efficacy of topical 2% mupirocin ointment for treatment of tympanostomy tube otorrhea caused by community-acquired methicillin resistant *Staphylococcus aureus*. *Int J Pediatr Otorhinolaryngol.* 2018;109:36-39.
9. Boon RJ, Beale AS, Sutherland R. Efficacy of topical mupirocin against an experimental *Staphylococcus aureus* surgical wound infection. *J Antimicrob Chemother.* 1985;16(4):519-526.
10. Canpolat F, Erkoçoğlu M, Tezer H, Kocabaş CN, Kandi B. Hydrocortisone acetate alone or combined with mupirocin for atopic dermatitis in infants under two years of age—a randomized double blind pilot trial. *Eur Rev Med Pharmacol Sci.* 2012;16(14):1989-1993.
11. Leyden JJ. Mupirocin: a new topical antibiotic. *J Am Acad Dermatol.* 1990;22(5 Pt 1):879-883.
12. Parenti MA, Hatfield SM, Leyden JJ. Mupirocin: a topical antibiotic with a unique structure and mechanism of action. *Clin Pharm.* 1987;6(10):761-770.
13. Gilbert M. Topical 2% mupirocin versus 2% fusidic acid ointment in the treatment of primary and secondary skin infections. *J Am Acad Dermatol.* 1989;20(6):1083-1087.
14. Wilkinson RD, Carey WD. Topical mupirocin versus topical neosporin in the treatment of cutaneous infections. *Int J Dermatol.* 1988;27(7):514-515.
15. Chua AN, Goldstein SL, Bell D, Brewer ED. Topical mupirocin/sodium hypochlorite reduces peritonitis and exit-site infection rates in children. *Clin J Am Soc Nephrol.* 2009;4(12):1939-1943.
16. Jervis-Bardy J, Boase S, Psaltis A, Foreman A, Wormald PJ. A randomized trial of mupirocin sinonasal rinses versus saline in surgically recalcitrant staphylococcal chronic rhinosinusitis. *Laryngoscope.* 2012;122(10):2148-2153.
17. Ng BHK, Tang IP, Narayanan P, Raman R, Carrau RL. Effects of nasal lavage with and without mupirocin after endoscopic endonasal skull base surgery: a randomised, controlled study. *J Laryngol Otol.* 2019;133(12):1059-1063.

18. Shikani AH, Khoueir N, Jabra-Rizk MA, Shikani HJ, Basaraba RJ, Leid JG. Topical therapy for refractory rhinosinusitis caused by methicillin-resistant *Staphylococcus aureus*: first report in a prospective series. *Auris Nasus Larynx*. 2018;45(5):994-999.
19. Solares CA, Batra PS, Hall GS, Citardi MJ. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant *Staphylococcus aureus* with mupirocin irrigations. *Am J Otolaryngol*. 2006;27(3):161-165.
20. Nsouli T, Diliberto N, Nsouli A, Nsouli S, Bellanti J. The empty nose syndrome (ENS): a diagnostic and therapeutic challenge for the allergist-immunologist. *Ann Allergy Asthma Immunol*. 2017;119(5):S88.
21. Fuller AT, Mellows G, Woolford M, Banks GT, Barrow KD, Chain EB. Pseudomonic acid: an antibiotic produced by *Pseudomonas fluorescens*. *Nature*. 1971;234(5329):416-417.
22. Thomas CM, Hothersall J, Willis CL, Simpson TJ. Resistance to and synthesis of the antibiotic mupirocin. *Nat Rev Microbiol*. 2010;8(4):281-289.
23. Tucaliuc A, Blaga AC, Galaction AI, Cascaval D. Mupirocin: applications and production. *Biotechnol Lett*. 2019;41(4-5):495-502.
24. Hetem DJ, Bootsma MC, Bonten MJ. Prevention of surgical site infections: decontamination with mupirocin based on preoperative screening for *Staphylococcus aureus* carriers or universal decontamination? *Clin Infect Dis*. 2016;62(5):631-636.
25. Bakkiyaraj D, Sritharadol R, Padmavathi AR, Nakpheng T, Srichana T. Anti-biofilm properties of a mupirocin spray formulation against *Escherichia coli* wound infections. *Biofouling*. 2017;33(7):591-600.
26. Bactroban [Prescribing information]. GlaxoSmithKline; March 2017.
27. Bactroban nasal ointment [Prescribing information]. GlaxoSmithKline; February 2020.
28. Bactroban cream [Prescribing information]. GlaxoSmithKline; February 2020.
29. Ward A, Campoli-Richards DM. Mupirocin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs*. 1986;32(5):425-444.
30. Noble WC. The uses and abuses of mupirocin. *J Dermatolog Treat*. 1991;1(6):317-319.
31. Reilly GD, Spencer RC. Pseudomonic acid—a new antibiotic for skin infections. *J Antimicrob Chemother*. 1984;13(3):295-298.
32. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10-52.
33. Tognetti L, Martinelli C, Berti S, et al. Bacterial skin and soft tissue infections: review of the epidemiology, microbiology, aetiopathogenesis and treatment: a collaboration between dermatologists and infectivologists. *J Eur Acad Dermatol Venereol*. 2012;26(8):931-941.
34. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18-55.
35. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. *Clin Infect Dis*. 2009;49(10):1541-1549.

36. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. *J Am Acad Dermatol*. 2008;58(2):185-206.
37. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fisccon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2017;6(6):CD011038.
38. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36 Suppl 1:e3280.
39. Banov D, Banov F, Bassani AS. Case series: the effectiveness of fatty acids from pracaxi oil in a topical silicone base for scar and wound therapy. *Dermatol Ther (Heidelb)*. 2014;4(2):259-269.
40. Allen LV. Betamethasone acetate 0.1%, mupirocin 1%, and nystatin 1% nipple ointment. *US Pharm*. 2011;36(6):44-45.
41. Williams KD. All-purpose nipple ointment: a compounding solution to common problems with breastfeeding. *Int J Pharm Compd*. 2010;14(6):484-486.
42. Furukawa M, Minekawa A, Haruyama T, et al. Clinical effectiveness of ototopical application of mupirocin ointment in methicillin-resistant *Staphylococcus aureus* otorrhea. *Otol Neurotol*. 2008;29(5):676-678.
43. Park KH, Lee CK. Mupirocin ointment prevents early post-tympanostomy tube otorrhea: a preliminary study. *Korean J Audiol*. 2012;16(3):130-133.
44. Isaacson G. Oxymetazoline, mupirocin, clotrimazole-safe, effective, off-label agents for tympanostomy tube care. *Ear Nose Throat J*. 2020;99(suppl 1):30S-34S.
45. Campbell D, Mudge DW, Craig JC, Johnson DW, Tong A, Strippoli GF. Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. *Cochrane Database Syst Rev*. 2017;4:CD004679.
46. McCann M, Moore ZE. Interventions for preventing infectious complications in haemodialysis patients with central venous catheters. *Cochrane Database Syst Rev*. 2010(1):CD006894.
47. Piraino B, Bernardini J, Brown E, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Perit Dial Int*. 2011;31(6):614-630.
48. Segal JH, Messana JM. Prevention of peritonitis in peritoneal dialysis. *Semin Dial*. 2013;26(4):494-502.
49. Coates T, Bax R, Coates A. Nasal decolonization of *Staphylococcus aureus* with mupirocin: strengths, weaknesses and future prospects. *J Antimicrob Chemother*. 2009;64(1):9-15.
50. Carlton DA, Beahm DD, Chiu AG. Topical antibiotic therapy in chronic rhinosinusitis: an update. *Int Forum Allergy Rhinol*. 2019;9(S1):S27-S31.
51. Kim JS, Kwon SH. Mupirocin in the treatment of Staphylococcal infections in chronic rhinosinusitis: a meta-analysis. *PLoS One*. 2016;11(12):e0167369.
52. Lee VS. Topical irrigations for chronic rhinosinusitis. *Immunol Allergy Clin North Am*. 2020;40(2):317-328.
53. Bactroban (mupirocin calcium) 2% cream medical review. Silver Spring, MD: Center for Drug Evaluation and Research, U.S. Food and Drug Administration;1997. Application number: NDA 50-746.

54. University of Utah Drug Information Service. Current drug shortages. American Society of Health-System Pharmacists (ASHP). <https://www.ashp.org/Drug-Shortages/Current-Shortages>. Accessed March 26, 2021.
55. Allen LV. Mupirocin 1% in normal saline nasal suspension. *US Pharm*. 2019;44(4):47-48.
56. Krismer B, Weidenmaier C, Zipperer A, Peschel A. The commensal lifestyle of *Staphylococcus aureus* and its interactions with the nasal microbiota. *Nat Rev Microbiol*. 2017;15(11):675-687.
57. Laux C, Peschel A, Krismer B. *Staphylococcus aureus* colonization of the human nose and interaction with other microbiome members. *Microbiol Spectr*. 2019;7(2).
58. Parlet CP, Brown MM, Horswill AR. Commensal Staphylococci influence *Staphylococcus aureus* skin colonization and disease. *Trends Microbiol*. 2019;27(6):497-507.
59. Jaspers ME, Breederveld RS, Tuinebreijer WE, Diederer BM. The evaluation of nasal mupirocin to prevent *Staphylococcus aureus* burn wound colonization in routine clinical practice. *Burns*. 2014;40(8):1570-1574.
60. Rangel SM, Paller AS. Bacterial colonization, overgrowth, and superinfection in atopic dermatitis. *Clin Dermatol*. 2018;36(5):641-647.
61. George S, Leasure AR, Horstmanshof D. Effectiveness of decolonization with chlorhexidine and mupirocin in reducing surgical site infections: a systematic review. *Dimens Crit Care Nurs*. 2016;35(4):204-222.
62. The REDUCE MRSA Trial Working Group. *Universal ICU Decolonization: An Enhanced Protocol*. Rockville, MD; Atlanta, GA: Agency for Healthcare Research and Quality; Centers for Disease Control and Prevention; September 2013. AHRQ Publication No. 13-0052-EF.
63. World Health Organization. *Global guidelines for the prevention of surgical site infection*. Geneva, Switzerland: World Health Organization (WHO);2016.
64. Kotloff KL, Shirley DT, Creech CB, et al. Mupirocin for *Staphylococcus aureus* decolonization of infants in neonatal intensive care units. *Pediatrics*. 2019;143(1):01.
65. Septimus EJ. Nasal decolonization: what antimicrobials are most effective prior to surgery? *Am J Infect Control*. 2019;47S:A53-A57.
66. van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing *Staphylococcus aureus* infections in nasal carriers. *Cochrane Database Syst Rev*. 2008(4):CD006216.
67. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195-283.
68. Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35(6):605-627.
69. American Academy of Orthopedic Surgeons. *American Academy of Orthopedic Surgeons clinical practice guideline on the diagnosis and prevention of periprosthetic joint infections*. Rosemont, IL: American Academy of Orthopedic Surgeons (AAOS); March 11, 2019.
70. Hansen D, Patzke PI, Werfel U, Benner D, Brauksiepe A, Popp W. Success of MRSA eradication in hospital routine: depends on compliance. *Infection*. 2007;35(4):260-264.
71. Ferraccioli GF, Salaffi F, Manganelli P. Mupirocin-resistant *Staphylococcus aureus*. *Lancet*. 1987;2(8555):388.

72. Rahman M, Noble WC, Cookson B. Mupirocin-resistant *Staphylococcus aureus*. *Lancet*. 1987;2(8555):387-388.
73. Antonov NK, Garzon MC, Morel KD, Whittier S, Planet PJ, Lauren CT. High prevalence of mupirocin resistance in *Staphylococcus aureus* isolates from a pediatric population. [published correction appears in *Antimicrob Agents Chemother*. 2015 Nov;59(11):7158]. *Antimicrob Agents Chemother*. 2015;59(6):3350-3356.
74. Hetem DJ, Bonten MJ. Clinical relevance of mupirocin resistance in *Staphylococcus aureus*. *J Hosp Infect*. 2013;85(4):249-256.
75. Khoshnood S, Heidary M, Asadi A, et al. A review on mechanism of action, resistance, synergism, and clinical implications of mupirocin against *Staphylococcus aureus*. *Biomed Pharmacother*. 2019;109:1809-1818.
76. Caffrey AR, Quilliam BJ, LaPlante KL. Risk factors associated with mupirocin resistance in methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect*. 2010;76(3):206-210.
77. Dadashi M, Hajikhani B, Darban-Sarokhalil D, van Belkum A, Goudarzi M. Mupirocin resistance in *Staphylococcus aureus*: a systematic review and meta-analysis. *J Glob Antimicrob Resist*. 2020;20:238-247.
78. Biedenbach DJ, Bouchillon SK, Johnson SA, Hoban DJ, Hackel M. Susceptibility of *Staphylococcus aureus* to topical agents in the United States: a sentinel study. *Clin Ther*. 2014;36(6):953-960.
79. Vivoni AM, Santos KR, de-Oliveira MP, et al. Mupirocin for controlling methicillin-resistant *Staphylococcus aureus*: lessons from a decade of use at a university hospital. *Infect Control Hosp Epidemiol*. 2005;26(7):662-667.
80. Walker ES, Levy F, Shorman M, David G, Abdalla J, Sarubbi FA. A decline in mupirocin resistance in methicillin-resistant *Staphylococcus aureus* accompanied administrative control of prescriptions. *J Clin Microbiol*. 2004;42(6):2792-2795.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily 1946 to February 17, 2021
- Date last searched: February 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 669

| | | |
|----|---|---------|
| 1 | mupirocin/ | 1256 |
| 2 | mupirocin\$.tw. | 1873 |
| 3 | (pseudomonic adj2 acid\$).tw. | 89 |
| 4 | supirocin\$.tw. | 1 |
| 5 | or/1-4 | 2154 |
| 6 | exp otitis/ | 28842 |
| 7 | administration, intranasal/ | 14966 |
| 8 | nasal sprays/ | 576 |
| 9 | otitis.tw. | 25568 |
| 10 | tympanitis.tw. | 47 |
| 11 | otic\$.tw. | 3658 |
| 12 | tympanic\$.tw. | 11467 |
| 13 | auricular\$.tw. | 11199 |
| 14 | (ear adj2 (drop? or effus\$ or infect\$ or inflamm\$ or secret\$ or solution?)).tw. | 5326 |
| 15 | nasal\$.tw. | 120261 |
| 16 | intranasal\$.tw. | 27703 |
| 17 | spray?.tw. | 29290 |
| 18 | or/6-17 | 225855 |
| 19 | and/5,18 | 737 |
| 20 | exp animals/ not humans/ | 4789299 |

| | | |
|----|------------------------------|-----|
| 21 | 19 not 20 | 721 |
| 22 | limit 21 to english language | 669 |

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other nonindexed citations and daily 1946 to February 17, 2021
- Date last searched: February 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 47

| | | |
|----|--|--------|
| 1 | mupirocin/ | 1256 |
| 2 | mupirocin\$.tw. | 1873 |
| 3 | (pseudomonic adj2 acid\$).tw. | 89 |
| 4 | supirocin\$.tw. | 1 |
| 5 | or/1-4 | 2154 |
| 6 | administration, topical/ | 38895 |
| 7 | administration, cutaneous/ | 22498 |
| 8 | skin absorption/ | 11856 |
| 9 | topical\$.tw. | 108931 |
| 10 | transcutaneous\$.tw. | 14885 |
| 11 | epicutaneous\$.tw. | 2047 |
| 12 | transdermal\$.tw. | 15057 |
| 13 | ((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw. | 11639 |
| 14 | exp gels/ | 53729 |
| 15 | emulsions/ | 18536 |
| 16 | suspensions/ | 7855 |
| 17 | liniments/ | 124 |
| 18 | ointments/ | 12872 |
| 19 | skin cream/ | 1105 |
| 20 | pharmaceutical solutions/ | 3318 |
| 21 | gel?.tw. | 312843 |
| 22 | emulsion?.tw. | 34490 |

| | | |
|----|----------------------|---------|
| 23 | suspension?.tw. | 111711 |
| 24 | liniment?.tw. | 148 |
| 25 | ointment?.tw. | 12178 |
| 26 | salve?.tw. | 345 |
| 27 | paste?.tw. | 12974 |
| 28 | unguent\$.tw. | 114 |
| 29 | lotion?.tw. | 2387 |
| 30 | cream?.tw. | 19576 |
| 31 | shampoo?.tw. | 1451 |
| 32 | solution?.tw. | 724727 |
| 33 | or/6-32 | 1349892 |
| 34 | drug combinations/ | 74313 |
| 35 | aloe/ | 1402 |
| 36 | aloe.tw. | 2847 |
| 37 | betamethasone/ | 5997 |
| 38 | bet?ade#ameta\$.tw. | 0 |
| 39 | bet?amet?a#on\$.tw. | 5097 |
| 40 | bet?a met?a#on\$.tw. | 137 |
| 41 | clobetasol/ | 1403 |
| 42 | clobetasol\$.tw. | 1142 |
| 43 | hyaluronic acid/ | 22113 |
| 44 | hyaluron\$.tw. | 37577 |
| 45 | ibuprofen/ | 9050 |
| 46 | ibuprofen\$.tw. | 14044 |
| 47 | ibuprophen\$.tw. | 29 |
| 48 | levoceterizin\$.tw. | 0 |

| | | |
|----|--|-------|
| 49 | lidocaine/ | 24662 |
| 50 | lidocain\$.tw. | 22184 |
| 51 | lignocain\$.tw. | 2955 |
| 52 | metronidazole/ | 12913 |
| 53 | metr#nida\$.tw. | 16390 |
| 54 | niacinamide/ | 12610 |
| 55 | amid\$ pp.tw. | 4 |
| 56 | nicotinamid\$.tw. | 21942 |
| 57 | niacetamid\$.tw. | 0 |
| 58 | niacinamid\$.tw. | 522 |
| 59 | niacin amid\$.tw. | 3 |
| 60 | nicamid\$.tw. | 0 |
| 61 | nicosedin\$.tw. | 0 |
| 62 | nicotamid\$.tw. | 14 |
| 63 | (nicotinic adj2 amid\$.tw. | 115 |
| 64 | nicotinoylamid\$.tw. | 1 |
| 65 | ni#otinsaureamid\$.tw. | 0 |
| 66 | nikotamin\$.tw. | 0 |
| 67 | vitamin\$ b3.tw. | 448 |
| 68 | vitamin\$ b 3.tw. | 54 |
| 69 | vitamin\$ pp.tw. | 164 |
| 70 | salicylic acid/ | 6729 |
| 71 | ((hydroxybenzoic or salicylic) adj2 acid\$.tw. | 15847 |
| 72 | anthranilic acid\$.tw. | 1392 |
| 73 | tranilast\$.tw. | 629 |
| 74 | exp triamcinolone/ | 9536 |

| | | |
|----|------------------------------|---------|
| 75 | t?iamcinolon\$.tw. | 7919 |
| 76 | t?iancinolon\$.tw. | 9 |
| 77 | tramcinolon\$.tw. | 3 |
| 78 | trancinolon\$.tw. | 0 |
| 79 | exp urea/ | 117000 |
| 80 | carbamid\$.tw. | 1527 |
| 81 | carbonamid\$.tw. | 16 |
| 82 | carbonyldiamid\$.tw. | 4 |
| 83 | karbamid\$.tw. | 0 |
| 84 | karbonamid\$.tw. | 0 |
| 85 | karbonyldiamid\$.tw. | 0 |
| 86 | harnstoff.tw. | 8 |
| 87 | urea.tw. | 85296 |
| 88 | uree.tw. | 107 |
| 89 | or/34-88 | 423035 |
| 90 | and/5,33,89 | 52 |
| 91 | exp animals/ not humans/ | 4789299 |
| 92 | 90 not 91 | 47 |
| 93 | limit 92 to english language | 47 |

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 890

| | | |
|----|---|---------|
| 1 | 'pseudomonic acid'/mj | 1408 |
| 2 | 'mupirocin*':ti,ab,tn | 2666 |
| 3 | (pseudomonic NEAR/2 acid*):ti,ab,tn | 128 |
| 4 | 'supirocin*':ti,ab,tn | 3 |
| 5 | #1 OR #2 OR #3 OR #4 | 3042 |
| 6 | 'otitis'/exp | 54553 |
| 7 | 'auricular drug administration'/de | 12 |
| 8 | 'intranasal drug administration'/de | 15084 |
| 9 | 'nose spray'/de | 3336 |
| 10 | 'otitis':ti,ab | 35258 |
| 11 | 'tympanitis':ti,ab | 79 |
| 12 | 'otic*':ti,ab | 5103 |
| 13 | 'tympanic*':ti,ab | 15498 |
| 14 | 'auricular*':ti,ab | 17161 |
| 15 | (ear NEAR/2 (drop\$ OR effus* OR infect* OR inflamm* OR secret* OR solution\$)):ti,ab | 6978 |
| 16 | 'nasal*':ti,ab | 168710 |
| 17 | 'intranasal*':ti,ab | 37135 |
| 18 | 'spray\$':ti,ab | 38977 |
| 19 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 | 321998 |
| 20 | #5 AND #19 | 1000 |
| 21 | [animals]/lim NOT [humans]/lim | 6170653 |
| 22 | #20 NOT #21 | 971 |

| | | |
|----|-------------------------------|-----|
| 23 | #20 NOT #21 AND [english]/lim | 890 |
|----|-------------------------------|-----|

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 334

| | | |
|----|--|--------|
| 1 | 'pseudomonic acid'/de | 7179 |
| 2 | 'mupirocin*':ti,ab,tn | 2666 |
| 3 | (pseudomonic NEAR/2 acid*):ti,ab,tn | 128 |
| 4 | 'supirocin*':ti,ab,tn | 3 |
| 5 | #1 OR #2 OR #3 OR #4 | 3042 |
| 6 | 'topical drug administration'/de | 84388 |
| 7 | 'cutaneous drug administration'/de | 756 |
| 8 | 'transdermal drug administration'/de | 9301 |
| 9 | 'skin absorption'/de | 8173 |
| 10 | 'topical treatment'/de | 13869 |
| 11 | 'topical*':ti,ab | 154253 |
| 12 | 'epicutaneous*':ti,ab | 3473 |
| 13 | 'transdermal*':ti,ab | 21975 |
| 14 | ((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab | 18398 |
| 15 | 'cream'/de | 9832 |
| 16 | 'gel'/exp | 81221 |
| 17 | 'liniment'/de | 257 |
| 18 | 'lotion'/de | 2969 |
| 19 | 'ointment'/de | 18290 |
| 20 | 'paste'/de | 2552 |
| 21 | 'salve'/de | 170 |
| 22 | 'suspension'/de | 28634 |

| | | |
|----|---|---------|
| 23 | 'emulsion'/exp | 47913 |
| 24 | 'shampoo'/de | 2345 |
| 25 | 'cream\$':ti,ab | 30601 |
| 26 | 'emulsion\$':ti,ab | 46598 |
| 27 | 'liniment\$':ti,ab | 242 |
| 28 | 'lotion\$':ti,ab | 4121 |
| 29 | 'ointment\$':ti,ab | 22020 |
| 30 | 'paste\$':ti,ab | 15489 |
| 31 | 'salve\$':ti,ab | 485 |
| 32 | 'unguent*':ti,ab | 242 |
| 33 | 'gel\$':ti,ab | 367839 |
| 34 | 'suspension\$':ti,ab | 148461 |
| 35 | 'shampoo\$':ti,ab | 2274 |
| 36 | 'solution\$':ti,ab | 896389 |
| 37 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 | 1719341 |
| 38 | 'drug combination'/de | 172258 |
| 39 | 'aloe'/exp | 3867 |
| 40 | 'aloe':ti,ab,tn | 4426 |
| 41 | 'betamethasone dipropionate'/de | 2847 |
| 42 | 'bet\$adesamet*':ti,ab,tn | 0 |
| 43 | 'bet\$adexamet*':ti,ab,tn | 0 |
| 44 | 'bet\$amet\$ason*':ti,ab,tn | 7698 |
| 45 | 'bet\$amet\$azon*':ti,ab,tn | 79 |
| 46 | 'bet\$a met\$azon*':ti,ab,tn | 1 |
| 47 | 'clobetasol propionate'/de | 4891 |
| 48 | 'clobetasol'/de | 2951 |

| | | |
|----|-----------------------------------|-------|
| 49 | 'clobetasol*':ti,ab,tn | 1903 |
| 50 | 'hyaluronic acid'/de | 45634 |
| 51 | 'hyaluron*':ti,ab,tn | 51186 |
| 52 | 'ibuprofen'/de | 51920 |
| 53 | 'ibuprofen*':ti,ab,tn | 20076 |
| 54 | 'ibuprophen*':ti,ab,tn | 60 |
| 55 | 'levocetirizine'/de | 1878 |
| 56 | 'levocetirizin*':ti,ab,tn | 726 |
| 57 | 'lidocaine'/de | 77705 |
| 58 | 'lidocain*':ti,ab,tn | 31108 |
| 59 | 'lignocain*':ti,ab,tn | 4131 |
| 60 | 'metronidazole'/de | 70964 |
| 61 | 'metranida*':ti,ab,tn | 64 |
| 62 | 'metronida*':ti,ab,tn | 24052 |
| 63 | 'nicotinamide'/exp | 16750 |
| 64 | 'amid* pp':ti,ab,tn | 7 |
| 65 | 'nicotinamid*':ti,ab,tn | 26495 |
| 66 | 'niacetamid*':ti,ab,tn | 0 |
| 67 | 'niacinamid*':ti,ab,tn | 817 |
| 68 | 'nicamid*':ti,ab,tn | 1 |
| 69 | 'nicosedin*':ti,ab,tn | 0 |
| 70 | 'nicotamid*':ti,ab,tn | 26 |
| 71 | (nicotinic NEAR/2 acid*):ti,ab,tn | 9656 |
| 72 | 'nicotinoylamid*':ti,ab,tn | 2 |
| 73 | 'nicotinsaureamid*':ti,ab,tn | 6 |
| 74 | 'nikotinsaureamid*':ti,ab,tn | 2 |

| | | |
|-----|--|--------|
| 75 | 'nikotamin*':ti,ab,tn | 0 |
| 76 | 'vitamin* b3':ti,ab,tn | 529 |
| 77 | 'vitamin* b 3':ti,ab,tn | 20 |
| 78 | 'vitamin* pp':ti,ab,tn | 297 |
| 79 | 'salicylic acid'/de | 26917 |
| 80 | ((hydroxybenzoic OR salicylic) NEAR/2 acid*):ti,ab,tn | 18966 |
| 81 | 'tranilast'/de | 1572 |
| 82 | 'anthranilic acid*':ti,ab,tn | 2027 |
| 83 | 'tranilast*':ti,ab,tn | 847 |
| 84 | 'triamcinolone'/de | 16336 |
| 85 | 'triamcinolone acetonide'/de | 15763 |
| 86 | 'tiamcinolon*':ti,ab,tn | 4 |
| 87 | 'triamcinolon*':ti,ab,tn | 11351 |
| 88 | 'tramcinolon*':ti,ab,tn | 12 |
| 89 | 'triancinolon*':ti,ab,tn | 21 |
| 90 | 'urea'/de | 87272 |
| 91 | 'carbamid*':ti,ab,tn | 1678 |
| 92 | 'carbonamid*':ti,ab,tn | 30 |
| 93 | 'carbonyldiamid*':ti,ab,tn | 6 |
| 94 | 'karbamid*':ti,ab,tn | 2 |
| 95 | 'karbonamid*':ti,ab,tn | 0 |
| 96 | 'karbonyldiamid*':ti,ab,tn | 0 |
| 97 | 'harnstoff':ti,ab,tn | 12 |
| 98 | 'urea':ti,ab,tn | 116957 |
| 99 | 'uree':ti,ab,tn | 156 |
| 100 | #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 | 705833 |

| | | |
|-----|---|---------|
| | OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 | |
| 101 | #5 AND #37 AND #100 | 365 |
| 102 | [animals]/lim NOT [humans]/lim | 6170653 |
| 103 | #101 NOT #102 | 356 |
| 104 | #101 NOT #102 AND [english]/lim | 334 |

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|-----------------------|-----------------------|-----------------------|
| Compounded drugs (medications prepared to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Do you prescribe or administer mupirocin to your patients?
 - Yes
 - No
3. Do you prescribe or administer mupirocin by any of the following dosage forms and/or routes of administration? (check all that apply)
 - Nasal spray
 - Otic
 - Topical dosage forms including but not limited to cream, emulsion, gel, ointment, solution, suspension
 - None of the above
4. I prescribe or administer mupirocin for the following conditions or diseases: (check all that apply)
 - Nasal infections
 - Superficial skin infections or wounds
 - Other (please explain) _____
5. I prescribe or administer mupirocin in combination with other active pharmaceutical ingredients as a multi-ingredient product.
 - Yes
 - No
6. I prescribe or administer mupirocin with my patients as the following: (check all that apply)
 - FDA-approved drug product
 - Compounded drug product
 - Other (please explain) _____
7. I use compounded mupirocin because: (check all that apply)
 - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
 - Patient allergies prevent me from using commercially available products (please explain) _____
 - Patient conditions prevent me from using commercially available products (please explain) _____
 - I am not aware of any commercially available products containing mupirocin

- Other (please explain) _____
- 8. Do you stock non-patient-specific compounded mupirocin at your practice?
 - Yes
 - No
 - I'm not sure
- 9. I obtain compounded mupirocin from the following: (check all that apply)
 - Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
- 10. What is your practice setting? (check all that apply)
 - Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
- 11. What degree do you hold? (check all that apply)
 - Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 2.2 Survey instrument for professional medical associations

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|-----------------------|-----------------------|-----------------------|
| Compounded drugs (medications prepared to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)

- Clotrimazole
- Fluconazole
- Itraconazole
- Ketoconazole
- Metronidazole
- Mupirocin
- Zinc oxide
- None of the above

3. Do you prescribe the compounded topical products that you selected in combination with other active pharmaceutical ingredients as a multi-ingredient product?

- Yes
- No
- I'm not sure

4. Why do you use the compounded topical products that you selected? (please check all that apply)

- Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
- Patient allergies prevent me from using commercially available products (please explain) _____
- Patient conditions prevent me from using commercially available products (please explain) _____
- I am not aware of any commercially available products containing these products
- Other (please explain) _____

5. Do you stock non-patient-specific compounded products at your practice?

- Yes
- No
- I'm not sure

6. I obtain compounded products from the following: (please check all that apply)

- Compound myself at my practice
- Have the product compounded by an in-house pharmacy

- Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
7. What is your practice setting? (please check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 2.3. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|-----------------------|-----------------------|-----------------------|
| Compounded drugs (medications prepared to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)

- Betamethasone acetate
- Betamethasone dipropionate
- Betamethasone sodium phosphate
- Cholestyramine resin
- Cimetidine
- Clobetasol propionate
- Clotrimazole
- Cromolyn sodium
- Dexamethasone sodium phosphate
- Diclofenac sodium
- Finasteride
- Fluconazole
- Fluticasone propionate
- Hydrocortisone
- Itraconazole
- Ketoconazole
- Lidocaine hydrochloride
- Methylprednisolone acetate
- Metronidazole
- Mupirocin
- Niacinamide
- Phytonadione (vitamin K1)
- Prilocaine
- Spironolactone
- Sulfacetamide sodium monohydrate
- Terbinafine hydrochloride
- Tetracaine hydrochloride
- Triamcinolone acetonide
- Zinc oxide

- None of the above
3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
 - Yes
 - No
 - I'm not sure
 4. Why do you use the compounded topical products that you selected? (please check all that apply)
 - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
 - Patient allergies prevent me from using commercially available products (please explain) _____
 - Patient conditions prevent me from using commercially available products (please explain) _____
 - I am not aware of any commercially available products containing these products
 - Other (please explain) _____
 5. Do you stock non-patient-specific compounded products at your practice?
 - Yes
 - No
 - I'm not sure
 6. I obtain compounded products from the following: (please check all that apply)
 - Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
 7. What is your practice setting? (please check all that apply)
 - Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
 8. What degree do you hold? (please check all that apply)
 - Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 2.4. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
 - Academic medical center
 - Acute care hospital
 - Children's hospital
 - Community hospital
 - Critical access hospital
 - Dialysis center
 - Federal government hospital
 - Health system
 - Inpatient rehabilitation center
 - Long-term acute care hospital
 - Outpatient surgery center
 - Rural hospital
 - Skilled nursing facility
 - Specialty hospital, please identify specialty(ies)
 - Trauma center
 - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
 - < 50
 - 50-99
 - 100-199
 - 200-299
 - 300-399
 - 400-599
 - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at <https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities>.
 - Yes
 - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
 - Backorders
 - Convenience
 - Cost
 - Need for concentrations not commercially available
 - Need for preservative-free products
 - Need for ready-to-use products
 - No FDA-approved products available
 - No onsite compounding facility
 - Onsite compounding facility not equipped to compound all necessary products
 - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
 - Nonsterile products
 - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
 - Cardioplegic solutions
 - Dermatologic preparations
 - Dialysate solutions

- Fluids
 - Ophthalmic preparations
 - Patient-controlled analgesia
 - Ready-to-use anesthesia syringes
 - Ready-to-use antibiotic syringes and/or bags
 - Ready-to-use electrolyte solutions
 - Ready-to-use vasopressor solutions
 - Total parenteral nutrition solutions
 - Other, please identify _____
7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
- Acetylcysteine
 - Adenosine
 - Aluminum potassium sulfate
 - Aspartic acid
 - Atenolol
 - Atropine
 - Baclofen
 - Betamethasone
 - Biotin
 - Bupivacaine
 - Calcium chloride
 - Caffeine sodium benzoate
 - Cholecalciferol
 - Chromium chloride
 - Clonidine
 - Dexamethasone sodium phosphate
 - Diclofenac
 - Gentamicin
 - Glycerin
 - Hydroxyzine
 - Ketamine
 - Levocarnitine
 - Lidocaine
 - Lorazepam
 - Magnesium sulfate
 - Manganese chloride
 - Methylprednisolone
 - Midazolam
 - Mupirocin
 - Norepinephrine
 - Ondansetron
 - Phytonadione
 - Potassium chloride
 - Potassium phosphate
 - Prilocaine
 - Proline
 - Propranolol
 - Ropivacaine
 - Sodium chloride
 - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 3. Survey distribution to professional associations

| Specialty | Association^a | Agreed/Declined, Reason for Declining |
|------------------|--|--|
| Anesthesiology | Society of Cardiovascular Anesthesiologists | Declined – failed to respond |
| Cardiology | American Academy of Cardiovascular Perfusion | Declined |
| | American Board of Cardiovascular Perfusion | Declined – failed to respond |
| | American Society of Extracorporeal Technology | Declined – failed to respond |
| Dermatology | American Academy of Dermatology | Declined – failed to respond |
| Naturopathy | American Association of Naturopathic Physicians | Agreed |
| Nephrology | American Society of Diagnostic and Interventional Nephrology | Declined |
| Ophthalmology | American Academy of Ophthalmology | Declined – failed to respond |
| | American Society of Cataract and Refractive Surgery | Agreed |
| | American Society of Retina Specialists | Declined |
| Podiatry | American Podiatric Medical Association | Agreed |
| Psychiatry | The International Society for Electroconvulsive Therapy and Neurostimulation | Agreed |
| Rheumatology | American College of Rheumatology | Agreed |
| Surgery | American Association of Neurological Surgeons | Declined – failed to respond |
| | American Association for Thoracic Surgery | Declined – failed to respond |
| | American College of Surgeons | Declined – failed to respond |
| | American Society for Reconstructive Microsurgery | Declined – failed to respond |
| Urology | Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction | Declined |
| Wound Care | Association for the Advancement of Wound Care | Declined – failed to respond |

^aAssociations that declined in Year 1 and/or Year 2 were not contacted in Year 3.