Summary Report

Gentamicin sulfate

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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
CIC	Clean intermittent catheterization
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
PCNL	Percutaneous nephrolithotomy
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States
URSL	Ureteroscopic lithotropsy
UTI	Urinary tract infection

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of gentamicin sulfate (gentamicin; UNII code: 8X7386QRLV), 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 gentamicin 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 healthcare practitioners were consulted to identify how gentamicin has been used historically and currently.[1-3] Assessments 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 gentamicin 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

Gentamicin was nominated for inclusion on the 503B Bulks List by Fagron, Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy. Gentamicin was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Gentamicin was nominated as a 10-80 mg/100 mL irrigation solution, in combination with neomycin and polymyxin B for treatment of bladder infection, and as 10 mg/mL or 40 mg/mL intravenous and intramuscular solution for treatment of bacterial infections.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of gentamicin.[6-9]

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

- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of gentamicin 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 the English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a usable 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 gentamicin; name variations of gentamicin 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 gentamicin. 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 comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: gentamicin; irrigation solution; and therapeutic or preventative use, or substances nominated for use in combination with gentamicin (refer to Appendix 1 for full search strategies). A literature review was not conducted for intravenous or intramuscular administration due to the availability of FDA-approved injectable gentamicin products. Results were limited to original research articles or conference abstracts in English language. Searches were conducted on August 31, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 31, 2020 for clinical practice guidelines that recommended the use of gentamicin and provided sufficient information on dosing and administration.

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

Study selection

Studies in which gentamicin 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 gentamicin was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which gentamicin 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 gentamicin; setting; total number of patients; number of patients who received gentamicin; patient population; indication for use of gentamicin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of gentamicin in a combination product; use and formulation of gentamicin in a compounded product; use of gentamicin 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 gentamicin 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 gentamicin. 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 gentamicin 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 to distribute 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 US 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

- Gentamicin is available as an FDA-approved product in the nominated dosage form and ROA.
- Gentamicin is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for gentamicin.
- Gentamicin is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Gentamicin sulfate	EQ 0.8-40 mg base/mL	Injectable	Injection	Prescription	9/7/1982

[a]Source: US FDA. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*
[b]If 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]
Gentamicin	40 mg/mL	Solution	Injection/infusion	Latvia	Prescription	5/10/2000
	10-40 mg/mL		Intramuscular	Australia	Schedule 4 - Prescription	8/13/1991
	1-40 mg/mL		Intravenous			
	1-3 mg/mL			Belgium	Prescription	2/1/2009
	10-40 mg/mL			Saudi Arabia	Prescription	–
Gentamicin sulfate	10-40 mg/mL	–	Injectable	Abu Dhabi	Active	–
	40-140 mg/mL 6%	Solution		Hong Kong	Prescription	6/1/1979
	40 mg/mL			Namibia	–	9/17/1997
	10-40 mg/mL			New Zealand	Prescription	1/14/1982
			Intramuscular	Canada	Prescription	12/20/2000
				Ireland	Prescription-only, non-renewable	3/9/1977
				UK	Prescription-only	12/20/1994
			Intravenous			
	1-40 mg/mL			Canada	Prescription	12/31/1995

				Ireland	Prescription-only, non-renewable	3/9/1977

Abbreviations: –, not provided.

[a]Medicine 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 usable 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.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 1161 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 975 titles and abstracts were screened. After screening, the full text of 62 articles was reviewed. Finally, 0 studies were included. Sixty-two studies were excluded for the following reasons: wrong study design (34 studies); gentamicin used as single-agent solution for bladder irrigation or instillation (14); gentamicin used in dosage form, ROA or combination that was not nominated (6); gentamicin used in FDA-approved dosage form or ROA (3); gentamicin not used clinically (2); gentamicin used in unspecified dosage form or ROA (1); duplicate study (1); unable to obtain full text (1).

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

Characteristics of included studies

No studies were included from the literature review.

Use of gentamicin

No studies were included from the literature review.

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 gentamicin.

Gentamicin is an aminoglycoside antibiotic derived from *Micromonospora purpurea* that was discovered in 1963.[10] Gentamicin exhibits bactericidal activity against aerobic Gram-negative bacteria including *Escherichia coli, Klebsiella pneumoniae,* and *Enterobacter* and *Pseudomonas* species.[10,11] Gentamicin is typically administered intravenously because there is minimal gastrointestinal absorption with oral administration.[10,11] Gentamicin is eliminated via the kidney, necessitating dose adjustments if used in patients with renal insufficiency.[7] Like other aminoglycoside antibiotics, gentamicin is associated with nephrotoxicity and ototoxicity, which manifests as proteinuria, decreased glomerular filtration rate, hearing loss, and vestibular dysfunction.[11] Given its spectrum of antimicrobial activity and route of elimination, gentamicin is very useful against the bacterial species that typically cause genitourinary infections, although the need for parenteral administration and concern for toxicity may limit its use.

Urinary tract infection (UTI) is infection of the upper (kidney and ureters) and/or lower (bladder and urethra) urinary tract with microorganisms. UTI can occur in any person of any age, but certain populations are more susceptible to developing UTIs and recurrent UTIs. Recurrent UTI in adults is defined as 2 or more infections in a 6-month period or 3 or more infections in a 12-month period.[12] Recurrent UTI in children or adolescents less than 16 years of age is defined as 2 or more episodes of acute pyelonephritis; 1 episode of acute pyelonephritis and 1 or more episodes of lower UTI; or 3 or more episodes of lower UTI.[12] Populations predisposed to UTI include people with an indwelling urinary catheter; neurogenic bladder; lower urinary tract dysfunction, anomalies and/or reconstruction; underlying conditions or treatments that cause immunosuppression; diabetes mellitus; and women.[13-17] Neurogenic bladder can occur in any condition that causes neurological damage or

degeneration resulting in disruption of the normal coordination between the autonomic and somatic nerves controlling bladder filling, storage, and emptying (micturition).[18] Common causes of neurogenic bladder include spinal cord injury, traumatic brain injury, multiple sclerosis, Parkinson's disease, cerebral palsy, and dementia. Patients with these conditions often have an indwelling urinary catheter or practice clean intermittent catheterization (CIC). Recurrent UTIs are uncomfortable for the patient, negatively impact patient and caregiver quality of life, and may require frequent visits to the doctor or emergency room and hospital admission.[15] Standard prevention and therapy for patients with recurrent UTIs includes oral antibiotics, behavioral modification (increased fluid intake and urination, attention to hygiene), and, for postmenopausal women, topical estrogen.[12,14,16] Oral antibiotic use is associated with disruption of the body's normal microflora, leading to side effects such as diarrhea. Oral antibiotic use may also contribute to the proliferation of antibiotic-resistant microorganisms.[16] Other prevention and treatment strategies include D-mannose, cranberry extracts, and probiotics, although evidence supporting the benefit of these strategies is lacking.[12,14] Management of patients with recurrent UTIs is often frustrating and at times unrewarding, which has prompted investigation of alternative prevention and treatment methods.

Intravesical administration, instillation or irrigation of medications in the bladder, has been used since the 1960s to treat a variety of conditions, including UTIs and bladder cancer. The advantage of intravesical administration is the ability to achieve high concentrations of a drug within the bladder while limiting the side effects associated with systemic administration of the drug.[9,13,19] The urothelium provides a durable barrier between the bladder and the rest of the body. While the urothelium does have some absorptive capacity, pharmacological factors, such as molecular size and lipophilicity, may also limit drug absorption.[19,20] Intravesical administration of antibiotics limits disruption of the body's normal microflora and may help reduce antibiotic resistance.[19,21]

Intravesical antibiotics have been used to prevent and treat UTIs since at least 1962 when Martin and Bookrajian described the use of dilute neomycin and polymyxin B to "continuously rinse" the bladder of women with indwelling urinary catheters who had undergone gynecological surgery.[22] The authors found that this combination significantly reduced the rate of UTI in these patients. Since the publication of this study, there have been several reports on the use of intravesical antibiotics for the prevention and treatment of UTIs. In a 1978 case-controlled study, Haldorson et al. reviewed patients with neurogenic bladder practicing intermittent urinary catheterization who received instillation of a neomycin solution after each catheterization (cases, 53 patients) to those who did not (controls, 55 patients).[23] The majority of patients in both groups also received methenamine mandelate or methenamine hippurate with ascorbic acid and/or oral antibiotics at some time during the study period. Fifty-three percent of patients who received intravesical neomycin developed bacteriuria during the study period; 17.8% of the once weekly urine cultures were positive. Forty-nine percent of patients in the control group developed bacteriuria during the study period; 14.1% of the weekly urine cultures were positive. The authors observed that the results "suggest that the use of neomycin is of doubtful value during intermittent urinary catheterization."[23] In 1978, Warren et al. published their findings from a randomized controlled trial of intravesical neomycin and polymyxin B irrigation in adult patients with closed catheter systems on the medical, surgical, and gynecological services at a city hospital.[24] Patients assigned to the treatment group (89) received at least 1000 mL per day of a neomycin sulfate 40 mg and polymyxin B sulfate 20 mg solution in 1 liter of normal saline via a closed drainage, triple-lumen urinary catheter. Patients in the control group (98) had indwelling closed drainage, double-lumen catheters and received no irrigation. Fourteen patients (16%) in the treatment group and eighteen patients (18%) in the control group acquired UTI during their hospital stay. The antibiotic sensitivities of the cultured microorganisms differed between the two groups; in

the treatment group, 6% and 31% of the isolated organisms were sensitive to neomycin and polymyxin B, respectively, compared to 58% and 72% of the organisms isolated in the control group. The authors decided that the irrigation protocol had no effect on the rate of acquired UTIs and increased antibiotic resistance among the infecting microorganisms. The authors hypothesized that the extra junction required for irrigation increased the risk of breaks in the integrity of the closed catheter system. The authors concluded that although "irrigation as it is now used cannot be recommended . . . more stringent procedures for catheter care, a different type of antimicrobial irrigant, greatly increased irrigant volumes or changes in the technic [*sic*] of irrigation might substantially lower infection rates in the patients receiving irrigation."[24] Rhame and Perkash[25] and Pearman[26] described their experience with bladder irrigation in patients with acute spinal cord injury. These studies utilized solutions of neomycin and polymyxin B or kanamycin and colistin for intravesical instillation. Pearman recommended that patients "should have kanamycin-colistin bladder instillations when they are being intermittently catheterised."[26]

Gentamicin has been used alone and in combination with other substances for intravesical irrigation in patients with neurogenic bladder, augmentation cystoplasty and/or urinary diversion, and other conditions predisposing to recurrent UTIs. Gentamicin's bactericidal activity against genitourinary pathogens and polar cationic nature, which limits diffusion across lipid membranes, make it the "ideal intravesical antibiotic."[21] Wan et al. investigated the systemic absorption of gentamicin in a rat fulgurated bladder model, canine model with vesicourethral reflux and elevated bladder pressures, and children with neurogenic bladder.[21] The rats had 1 mL of a gentamicin solution instilled into their bladder after cystotomy and fulguration with electrocautery. Serum gentamicin levels 30 minutes after instillation showed systemic absorption of gentamicin in 3 of 7 rats (43%), but levels were in the low-nontoxic range in all of these animals. The canines with vesicourethral reflux had undetectable serum levels of gentamicin after forceful infusion of a gentamicin solution into the bladder, and no change in serum creatinine 3 days after the infusion. In the in vivo study, 10 children who performed CIC for neurogenic bladder were placed on a regimen of 30 to 60 mL of gentamicin solution (480 mg/L saline) twice a day for 1 week. Prior to initiation of treatment, 3 children had *E. coli* growth on urine culture; 0 children had growth on urine culture after treatment. None of the children had detectable serum levels of gentamicin 30 minutes after instillation nor did any of the children have a change in serum creatinine during treatment. The authors stated that intravesical gentamicin was a safe and effective treatment that should be considered for prevention of UTI in patients who perform CIC.

In a 1987 case report, McGuire and Savastano described their experience with intravesical instillation of gentamycin or garamycin in 4 women with intractable UTIs.[27] Three women received 20 to 30 mL of a gentamicin solution (gentamicin 240 mg in 1 L saline) instilled via catheter 4 times a day for 3 to 18 months; one woman received a garamycin solution. All 4 women experienced improvement in their symptoms and had negative urine cultures while receiving intravesical treatment. In some patients, the positive effects persisted after cessation of treatment while in others, symptoms and infection returned. Since the publication of this case report, there have been several additional case reports detailing the use of intravesical gentamicin in patients with recurrent UTIs. The treatment regimens in these reports have used gentamicin solutions ranging from 0.8 mg/mL to 4 mg/mL administered one to three times a day for short-term treatment and/or long-term prophylaxis.[9,28-30] In all of the patients described in these reports, lower urinary tract symptoms improved and infection resolved with the administration of intravesical gentamicin, with no side effects. All the patients in these reports were > 65 years of age and in some cases, intravesical therapy reduced or eliminated emergency department visits and hospital admissions.

Multiple retrospective reviews and one prospective noncontrolled trial have utilized intravesical gentamicin for the prevention and treatment of recurrent UTI in adults. In two abstracts presented in 2014, 14 patients with recurrent UTI were treated with intravesical gentamicin (80 mg) once a day for an average of 16 months.[31,32] Serum gentamicin levels were less than 0.3 ng/mL on day 7 in all patients. Twelve patients continued intravesical therapy: 7 of these patients had no further UTIs, 1 patient had one *Enterococcus* UTI that was resistant to gentamicin, and 4 patients had multiple UTIs. The authors of this study concluded that in "patients who have multiple UTIs refractory to conventional treatment, intravesical gentamicin is effective in reducing the frequency of infections."[31,32] The authors of these two abstracts published their findings in a 2017 article, which described their experience with intravesical gentamicin administration in 27 patients with lower urinary tract dysfunction and recurrent UTI.[13] Patients instilled gentamicin (80 mg dissolved in 50 mL sterile water or 0.9% sodium chloride) once a day for 2 to 67 months. Twenty-two patients remained on the once-a-day regimen; 1 patient decided to instill gentamicin twice a week, 1 patient instilled gentamicin when she became symptomatic, 1 patient instilled gentamicin every other day, and 1 every 5 days. Twenty-three of the 27 patients had documented serum gentamicin levels, all of which were less than 0.3 ng/mL. Eighteen patients had breakthrough UTIs during the first 12 months of intravesical therapy. The authors' conclusions were similar to before, mainly that intravesical gentamicin reduced UTI frequency in patients refractory to conventional therapy, with no systemic side effects.

Cox et al. shared their experience using intravesical gentamicin in patients with neurogenic bladder who practice intermittent self-catheterization and have frequent symptomatic UTIs.[16] Twenty-two patients were followed for 6 months before and 6 months after initiation of prophylactic intravesical gentamicin instillation (30 to 60 mL of a compounded gentamicin 480 mg/1 L normal saline solution) once each evening. The median number of symptomatic UTIs decreased from 4 in the 6 months before initiation of intravesical therapy to 1 in the 6 months after. The median number of antibiotic courses decreased from 3.5 to 1, and the median number of days on oral antibiotics decreased from 15 days before starting intravesical therapy to 5 after. The proportion of multidrug resistant microorganisms on urine culture decreased significantly from 58.3% before intravesical therapy to 47.1% after; the rate of gentamicin resistance did not increase after initiation of therapy. The authors noted that intravesical therapy decreased the frequency of symptomatic UTIs and need for oral antibiotics in patients with neurogenic bladder, and called for larger, prospective, placebo-controlled trials to confirm these findings.

In a 2017 abstract, Harmon and Hassoun reported the use of antibiotic bladder irrigation in 39 patients with recurrent UTI due chronic urinary catheterization.[33] Almost half of these patients had a neurogenic bladder; 22 had an indwelling urinary catheter, 12 had a suprapubic catheter and 5 practiced self-catheterization. Sixty-seven percent of the patients utilized a gentamicin solution for bladder irrigation. Twenty-six patients (67%) experienced alleviation of symptoms and success with intravesical therapy; 4 patients had improvement in their symptoms but did not meet the criteria for complete success. The authors concluded that "[u]se of antibiotic bladder irrigation was successful in reducing symptom frequency and requirement of systemic antibiotics."[33] In two abstracts published in 2019, 11 patients with recurrent UTIs refractory to conventional therapy received intravesical gentamicin (80 mg in 50 mL normal saline) once a day for an average of 7 months (range 2 to 18 months).[34,35] Ninety-one percent (10) of these patients experienced an improvement in pelvic pain after initiation of intravesical gentamicin instillation. The number of symptomatic UTIs decreased from 8.3 prior to intravesical therapy to 1.8 after; the number of multidrug resistant organisms decreased from a mean of 7.38 before starting intravesical therapy to a mean of 1 after. Recently,

Chernyak and Salamon described their experience with in-office intravesical aminoglycoside instillation in 12 postmenopausal women with recurrent UTIs.[36] The women received either gentamicin (11 patients, 80 mg in 60 mL normal saline) or tobramycin (1 patient), based on the sensitivity profile of their most recent urine culture, twice a week for 3 weeks. The average number of instillations was 8.42, the range was 6 to 12. The authors reported a statistically significant decrease in the rate of UTI from a median of 2.5 in the 6 months before intravesical treatment to a median of 1.5 in the 6 months after treatment. The median number of antibiotics in the resistance profile decreased from 8.5 before intravesical treatment to 0 after treatment. No adverse effects were noted. The authors suggested that "intravesical instillations offer a promising therapy for the treatment of recurrent UTIs in postmenopausal women who failed oral antibiotic therapy."[36]

The one prospective trial of intravesical gentamicin therapy was published in 2019.[37] In this trial, patients with recurrent UTI with multidrug resistant bacteria received intravesical gentamicin (80 mg in 20 mL 0.9% sodium chloride) once a day for 2 weeks, then every other day for 10 weeks, and finally twice a week for 12 weeks for a total of 24 weeks of therapy. Sixty-three patients were enrolled in the study, of whom 57 received gentamicin; the remaining 6 patients received either tobramycin or amikacin due to gentamicin resistance on baseline culture. The mean number of UTIs decreased significantly from 4.8 ± 1.5 in the 6 months before intravesical therapy to 1.2 ± 1.3 in the 6 months after. Twenty-six patients (41%) had no episodes of UTI during treatment; 52 patients (85%) had a 50% reduction in their rate of UTI. The rate of multidrug resistance decreased from 78% of UTIs before intravesical therapy to 23% after therapy. Two patients had a minor increase in serum creatinine, which normalized at the next visit. Two patients noted hearing loss during therapy, but this was unlikely to have been related to the intravesical gentamicin because the serum gentamicin levels in these patients were undetectable. The study authors noted that in addition to intravesical gentamicin instillation being "a valuable treatment option," it can also be used for diagnostic purposes because patients with persistent, gentamicin-sensitive bacteriuria between instillations are likely to have upper UTIs.[37]

Several studies have described the use of intravesical gentamicin for prevention and treatment of UTI in children. In 2004, Hensle and colleagues shared their experience with an intravesical irrigation protocol for preventing reservoir calculi in patients who had undergone augmentation cystoplasty and/or urinary diversion.[38] Patients received 240 mL of saline twice a week and 120 to 240 mL of a gentamicin solution (240 to 480 mg/L saline) twice a week. Prior to the initiation of this protocol, 39 of 91 patients (43%) had reservoir calculi after surgery; after instituting the protocol, 3 of 42 patients (7%) developed reservoir calculi. The authors indicated that "the use of a routine irrigation protocol had a significant effect in reducing the number of reservoir calculi after urinary tract reconstruction when bowel was used as part of the reconstruction."[38] In a study published in 2006, the authors reported their findings from treating 80 children with gentamicin bladder irrigation over a 5-year period.[7] The majority of patients in the study had been diagnosed with neuropathic bladder (54); almost half of the patients (39) had undergone augmentation cystoplasty and/or creation of a new urethra. The hospital pharmacy compounded a gentamicin solution (120 mg/250 mL normal saline), which was dispensed in 30 mL syringes for administration 1 to 2 times a day. Median duration of treatment was 90 days, range was 3 to 1095 days. Twenty-one patients (26%) experienced a symptomatic breakthrough UTI while receiving intravesical treatment; 5 of these patients had microorganisms that were resistant to gentamicin. No patients had a serum gentamicin level greater than 0.4 mcg/mL during the study period, and no adverse events were reported. The authors of this study concluded that "[g]entamicin bladder irrigations are a helpful adjunct in the management of complex pediatric urological cases involving recurrent symptomatic bacteriuria."[7] Traxel et al.

compared the incidence of UTI after renal transplantation in children who had undergone augmentation cystoplasty prior to surgery (cases, 17 patients) to those who had not (controls, 17 patients).[39] Among the cases, 15 patients remained on prophylactic antibiotics after surgery, 10 received oral antibiotics, 4 received intravesical gentamicin irrigation, and 1 received oral antibiotics and intravesical gentamicin irrigation, with a median follow-up of 7.7 years after transplantation. In the control group, all 17 patients remained on prophylactic antibiotics after surgery: 12 received oral antibiotics, 2 received intravesical gentamicin irrigation, and 3 received oral antibiotics and intravesical gentamicin irrigation, with a median follow-up of 6.1 years. Among the cases, the cumulative UTI rate before initiation of gentamicin irrigation was 0.56 UTI per year; the rate was 0 UTI per year after initiation of gentamicin irrigation (this rate was calculated after removal of 1 particularly noncompliant patient from this group). In the control group, the cumulative UTI rate before starting gentamicin irrigation was 0.23 UTI per year; the rate was 0.20 UTI per year after starting gentamicin irrigation. The authors concluded that there did not appear to be an increased risk of UTI in patients who had augmentation cystoplasty prior to renal transplantation compared to those who did not. They attributed the low incidence of UTI, in part, to their aggressive prophylactic strategy, including intravesical gentamicin irrigation. Diaz et al. also utilized intravesical gentamicin irrigation in pediatric patients with congenital lower urinary tract anomalies who received a kidney transplant.[40] In a 2021 retrospective review, Marei and coauthors described their use of intravesical gentamicin for the prevention and treatment of UTIs in pediatric patients with complex urinary tract anomalies, including neuropathic bladder, anorectal malformations, bladder exstrophy, and posterior urethral valves.[20] Intravesical gentamicin instillation was instituted in patients with an indwelling urinary catheter, or who practiced CIC, and experienced recurrent symptomatic breakthrough UTI or symptomatic UTI with positive culture and resistance to oral antibiotics. The gentamicin solution (8 mg/20 mL or 20 mg/50 mL) was instilled into the bladder and allowed to remain for 1 hour prior to emptying, once a day or every other day for prevention or twice a day for 7 days for treatment. Twenty-four cases were included in the review; 19 patients received the prophylactic regimen and 14 received the treatment regimen. Overall, 42% of patients (8) had a breakthrough UTI while receiving the prophylactic regimen; 85% of patients (12) had successful clearance of their UTI within 7 days while receiving the treatment regimen. Among the study participants, 11 were at high risk for chronic renal insufficiency or end-stage renal disease, 3 were at moderate risk, and 10 were at low risk. One patient had a detectable serum gentamicin level during the study period, but this patient had mistakenly received an intravenous dose of gentamicin 24 hours prior to the blood draw. During the study period, 17 patients underwent audiology testing; 2 of these patients had abnormal results, 1 due to recurrent ear infection and the other due to known hypoplasia of the vestibulocochlear nerve. The authors concluded, "in the appropriately selected patients, [intravesical gentamicin instillation] is an effective modality to treat and prevent UTIs, thus diversifying our available options in complex paediatric urology patients."[20] In the future, the authors considered increasing the prophylactic regimen to once a day (rather than 3 times per week), not measuring serum gentamicin on a regular basis unless indicated, and pre-packaging syringes for home administration.

Gentamicin solutions have also been used for irrigation of the upper urinary tract during percutaneous nephrolithotomy (PCNL) and ureteroscopic lithotripsy (URSL). Mikhail et al. described the administration of a gentamicin solution (80 mg in 3 L normal saline), after administration of a betadine solution, via ureteral catheter for renal pelvis sterilization in 32 patients undergoing PCNL.[41] A randomized controlled trial investigated the effect of irrigation with a gentamicin solution versus normal saline on the rate of postoperative fever (as an indicator of possible infection) in 134 patients undergoing PCNL and URSL. A total of 12 patients developed a fever postoperatively; the duration of fever was shorter in patients who received gentamicin irrigation compared to those who received

normal saline. The authors recommended a study with a larger number of patients to validate their findings.[42]

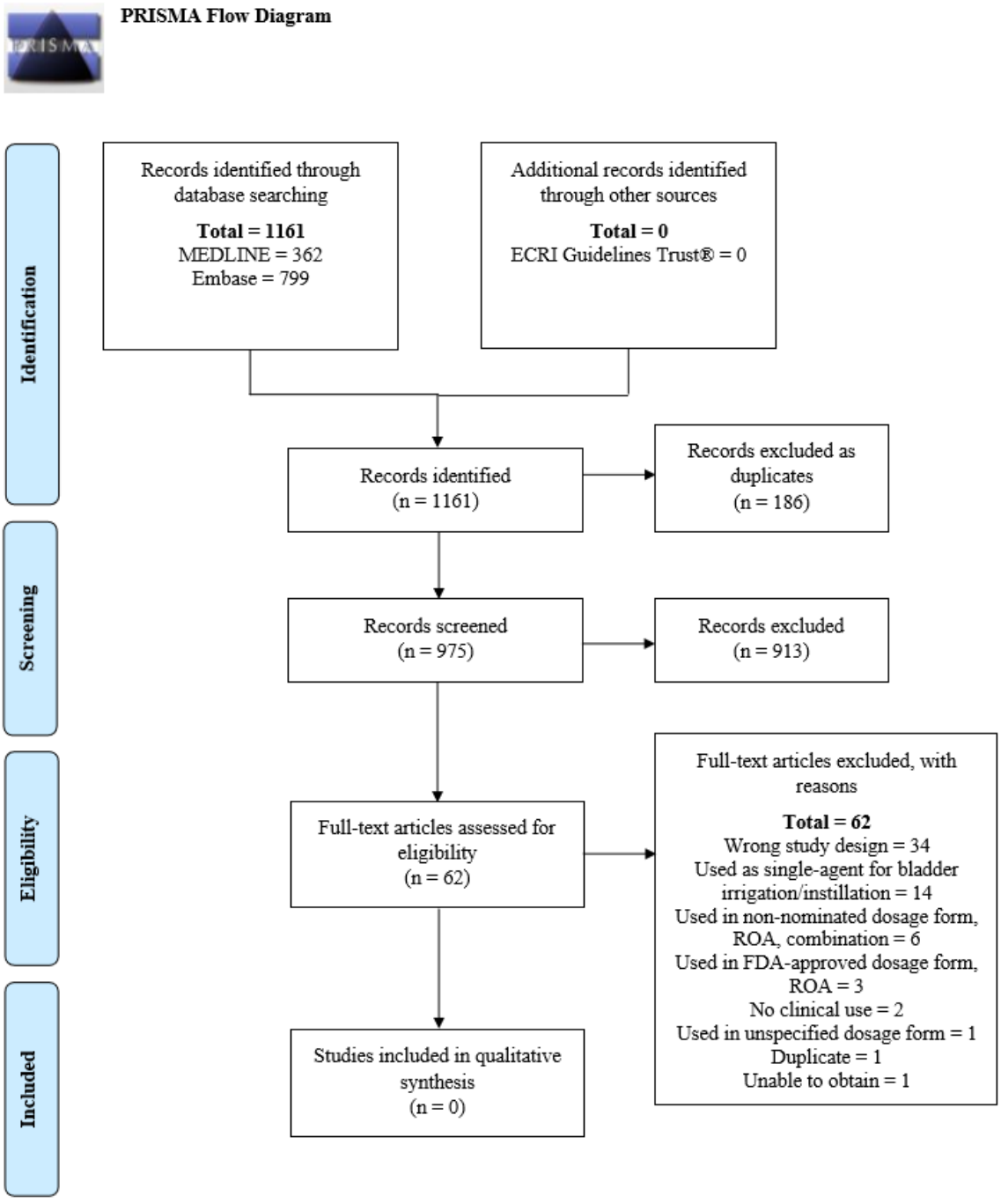
No studies were found that reported the use of gentamicin in combination with neomycin and polymyxin B as an intravesical irrigation solution. However, a 2014 article in *U.S. Pharmacist* provided a formulation for the preparation of this combination as a bladder irrigation solution: gentamicin 10 mg, neomycin sulfate 50 mg, and polymyxin B 10,000 units in 100 mL sterile water.[43] The author cautioned that this is a high-risk preparation and bladder irrigation solutions must be prepared according to USP General Chapter <797> standards on compounding sterile preparations. Several studies described the use of gentamicin in combination with other substances for intravesical instillation. In a 2009 retrospective study, Tseng et al. described the use of a "bladder cocktail" in cervical cancer patients with radiation cystitis.[44] Twenty-three patients had a solution of Solu-Cortef®, heparin, lidocaine, sodium bicarbonate and/or gentamicin instilled into the bladder once a week for at least 6 months. Twenty-one patients (91.3%) experienced significant improvement or complete resolution of their hematuria. The authors proclaimed that "[t]he success of this innovation enables the use [of] sequential bladder cocktail installation as the primary treatment for cervical cancer patients with retractable radiation cystitis."[44] A 2011 case series reported the intravesical administration of a gentamicin and prostaglandin F2 alpha solution in 68 diabetic patients with neuropathic underactive bladder.[45] Overall, 65-80% of patients experienced improvement in their urinary symptoms while receiving this combination solution. The author concluded, "Timed regular prostaglandin F2 alpha as intravesical local therapy is considered a minimally invasive, simple, cheap, effective therapeutic option for diabetic underactive cystopathy."[45] In another case series, 35 patients with neurogenic bladder or bladder hypocontractility and recurrent UTIs instilled a solution of gentamicin and glycosaminoglycans (hyaluronic acid, chondroitin sulfate, or hyaluronic acid associated with chondroitin sulfate) during routine intermittent catheterization for 1 year, with the goal of eliminating infection and reducing inflammation.[46] All patients experienced improvement in symptoms while receiving this therapy; urine culture became negative in 22 patients. In a 2014 randomized controlled trial, 60 women with urethral syndrome (idiopathic cystitis) and trigonitis received either a intravesical gentamicin and dexamethasone solution twice a week for 7 weeks or oral Cistiquer, a phytotherapeutic agent, once a day for 7 weeks.[47] Although both treatment groups experienced "significant and comparable" improvement, patients who received Cistiquer reported better improvement of urinary discomfort and had a lower rate of adverse events than those who received intravesical gentamicin and dexamethasone. In a review on interstitial cystitis, the authors noted that "intravesical 'cocktails' using heparin, lidocaine and bicarbonate with or without gentamicin and/or glucocorticoids are widely used" in the management of patients with interstitial cystitis.[48] Interstitial cystitis, also known as painful bladder syndrome and bladder pain syndrome, is a chronic condition characterized by pain and a feeling of increased pressure in the bladder and surrounding areas, such as the urethra, pelvis and lower abdomen.[48] Treatment of interstitial cystitis typically includes behavioral and dietary modification, oral medications such as amitriptyline, and intravesical therapy, including hydrodistension and instillation of a variety of substances.[48]

In the 2009 International Clinical Practice Guideline from the Infectious Diseases Society of America on the management of catheter-associated UTI, routine catheter irrigation with antimicrobials to reduce or eliminate catheter-associated bacteriuria or catheter-associated UTI in patients with indwelling catheters was not recommended, nor was systemic or intravesical antimicrobial administration at the time of catheter placement, replacement, or removal.[17] The guideline indicated that "catheter irrigation with antimicrobials may be considered in selected patients who undergo surgical procedures and short-term catheterization to reduce CA[catheter-associated] bacteriuria."[17]

The authors concluded that there was insufficient evidence to determine whether catheter irrigation and prophylactic antimicrobials reduce catheter-associated UTI and bacteremia. The 2016 European Association of Urology guidelines on neuro-urology stated that bladder irrigation has not been proven effective in the management of recurrent UTI in patients with neuro-urological conditions.[49] A 2018 systematic review and practice policy statement on UTI prevention in adults with spina bifida, conducted on behalf of the Neurogenic Bladder Research Group, recommended that based on the few observational studies available "clinicians may use intravesical gentamicin instillation for the prevention of UTI in adults with spina bifida" (Oxford Level of Evidence, 3; Grade of Recommendation, C).[50] In another 2018 systematic review, Pietropaolo et al. examined the effectiveness of intravesical antimicrobial instillation for the prevention and treatment of recurrent UTIs.[51,52] Eleven studies with 285 patients were included; 117 patients (41%) received intravesical antibiotics for prevention of recurrent UTI and 168 patients (59%) received intravesical antibiotics for the treatment of recurrent UTI. All of the included studies, except for 1, were classified as observational. Gentamicin was used in 7 of the 11 included studies, neomycin and polymyxin B were used in 2 studies, neomycin alone in 1 study and colistin alone in 1 study. Overall, 78.2% (223) of patients experienced a reduction in symptomatic UTIs with the intravesical administration of antimicrobials. The short term (3-6 months) success rates in the prevention and treatment groups were 71% (120) and 88% (103), respectively; the discontinuation rates in each group were low at 8% (14) and 5% (6) in the prevention and treatment groups, respectively. In patients who received gentamicin as the intravesical agent, the discontinuation rate was 5% (9) while the discontinuation rate was 11% (11) in patients who received other non-gentamicin antimicrobials. Side effects in all patients were minor and included allergy, suprapubic discomfort, autonomic dysreflexia, upper respiratory infection, and diarrhea. The authors of this review concluded, "[i]ntravesical antimicrobial instillation seems to be a relatively safe and effective method for the prophylaxis and treatment of recurrent UTIs, especially in the short term," which gives clinicians an alternative treatment option "in high-risk patients predisposed to UTIs where all other forms of systemic treatments have failed."[52]

Overall, the evidence for intravesical administration of antibiotics appears promising, but at present consists primarily of descriptive and observational studies in a small number of patients with a variety of conditions. The advantages of intravesical antibiotic administration are localized delivery of a high concentration of drug within the bladder and reduction of side effects and/or toxicity associated with systemic antibiotic administration. Intravesical therapy may be limited by the need for catheterization. Many of the published reports of intravesical antibiotic administration were conducted in patients who already practiced CIC or had an indwelling urinary catheter, although a few reports described intravesical therapy in neurologically intact patients who were either trained to perform self-catheterization or received in-office catheterization and instillation. Young or older patients may lack the dexterity necessary to perform self-catheterization.

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

No studies were included

Table 4. Number of studies by country

No studies were included

Table 5. Summary of included studies

No studies were included

Table 6. Dosage by indication – US

No studies were included

Table 7. Dosage by indication – non-US countries

No studies were included

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Gentamicin sulfate 10-80 mg / Neomycin / Polymyxin B – bladder irrigation	0

Table 9. Compounded products – US

No studies were included

Table 10. Compounded products – non-US countries

No studies were included

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. Two SMEs discussed gentamicin. Both SMEs were medical doctors. The SMEs specialized and/or were board-certified in urology, working in academic medical institutions. The SMEs had been in practice for 13 and 19 years.

Gentamicin was nominated as a bladder irrigation solution in combination with neomycin and polymyxin B. Gentamicin was also nominated as an intramuscular and intravenous injectable solution. The two SMEs who specialized in urology used gentamicin as a single-agent bladder instillation solution as a preventative therapy in patients with recurrent UTIs. This solution is usually utilized in patients who already practiced intermittent self-catheterization, thus eliminating this barrier to use, and for whom conventional preventative therapies, such as hygiene, increased water intake, more frequent catheterization, and oral antibiotics had not worked. One SME noted that they typically initiate therapeutic gentamicin bladder instillation only in patients who have experienced a substantial number of because bladder instillations are one additional step that a patient needs to complete each day. This SME remarked, "It's typically for those patients that are getting upwards of 10, 15, 20, 30 UTIs a year. Those are the patients where doing a daily intervention is worthwhile for them, and in neurogenic patients—so, patients who catheterize themselves—the data is very, very weak on daily oral antibiotics." The population in whom gentamicin bladder instillations are used as a preventative therapy included patients with congenital bladder abnormalities, spinal cord injury, radiation injury, and surgically altered urinary tracts. One SME observed that in patients with non-neurogenic bladders, other preventative therapies, such as estrogen and cranberry, often worked. This SME commented that it would take many more steps to get to bladder instillation therapy in these patients because they are not already self-catheterizing. The other SME who specialized in urology agreed with these statements, commenting that patients who utilize gentamicin bladder instillations are "a more complex patient population. These are not your recurrent UTI off the street, menopausal ladies that are otherwise at target, but they get a little bit of burning here and there. These are usually people who've been hospitalized for systemic infections related to their UTI." This SME noted that the need to catheterize was a barrier to the use of bladder instillation therapy in patients who did not practice CIC. The SME stated, "[T]he barrier really to the therapy is not the medicine, it's the logistics of, 'we don't have any way to get this into your bladder unless you [catheterize] in some way.' . . . I have seen patients who I would have liked to use the therapy in, but they either don't want to or aren't capable of doing the [catheterization] themselves." One SME said that gentamicin bladder instillation therapy is not typically used in patients with indwelling urinary catheters because this population tends to be more debilitated and there is less literature on the use of this therapy in these patients.

When used as a preventative therapy in patients with recurrent UTIs, gentamicin bladder instillation solution is typically administered as 30 to 60 mL of a 480 mg/L solution once a day, usually at night, and remains in the bladder until the next catheterization. One SME stated that they usually recommend this preventative routine for 6 months to 1 year and then reassess the patient. In this SME's experience, at initial reassessment most patients prefer to continue the bladder instillations. This SME commented that data has shown that when bladder instillations are discontinued in patients with non-neurogenic bladders, these patients usually return to their baseline risk for UTIs within one month. In the SME's own practice, some patients discontinued gentamicin bladder instillations and were fine while others restarted within a week. The SME suggested that in those patients who restarted, gentamicin bladder instillations offered the dual benefit of reducing bacteriuria and the incidence of UTIs. This SME remarked:

> People who have chronic bacteria have chronic stinky, smelly, gross-smelling, cloudy, slimy urine, and the gentamicin makes their urine clear. Even though that's not the reason we're doing it, we're preventing real UTIs, but these patients notice within a week that their urine is nasty, and they're wanting to go back on it.

The SME also observed that "it's very rare that I suggest quitting and someone actually does it." The other SME who specialized in urology had a similar experience with patients who utilized gentamicin bladder instillations for UTI prevention. This SME stated that the duration of the preventative therapy depended on the patient's initial response:

> So it depends a little bit on if they're having breakthrough. And so let's say someone's getting six UTIs a year and on [gentamicin bladder instillations], they're getting one or two, but they're still having them. Then I usually keep them on that indefinitely with further workup, more planning. Let's say we put someone that's getting six UTIs a year on gent instillations and over the first six months, they have no breakthroughs, then a lot of those times I'll take those people off. And so, it depends a little bit on their initial response, and if they initially respond really well and they're somebody who is healthy enough and reliable to give a trial off of the medications.

This SME also had many patients who elected to continue gentamicin bladder instillations as a preventative therapy because "if we do get them infection-free for a period of time, they're so afraid of losing that freedom, that they very strongly wish to remain on it," and these patients are "so afraid of going back to the way they were."

The SMEs had not witnessed resistance to gentamicin in patients who had breakthrough UTIs while on preventative gentamicin bladder instillation therapy. One SME observed:

> [T]he UTIs that patients get while on [gentamicin] are actually more sensitive than before because you're not subjecting them to systemic antibiotics, so their gut flora's not exposed to antibiotics. Hence, their gut flora remains sensitive, so they become multidrug sensitive UTIs that can be treated with Bactrim [sulfamethoxazole/trimethoprim], or treated with Cipro [ciprofloxacin], or treated with Macrobid [nitrofurantoin], as opposed to meropenem. So, they become more sensitive over time, actually.

The other SME commented that since the gentamicin only remains in the bladder for a period of time during the day and the rest of the time catheterization is introducing new inoculations of bacteria that have not been exposed to gentamicin, the probability of a patient having only gentamicin-resistant bacteria in their bladder at any one time is relatively low. This SME also noted that gentamicin-resistant infections also occur in patients who have not been exposed to the drug. In addition to the overall low level of gentamicin resistance in patients on gentamicin bladder instillations, one SME commented that due to concerns about adverse side effects, gentamicin is not typically a first-line treatment for infections that require parenteral antibiotics. The SME stated:

> And the nice thing, I guess, is that gentamicin's such a toxic drug to give IV [intravenously] that no one ever wants that to be their IV or IM [intramuscular] option anyway. And so, it's not like the ER is rushing to give them . . . gentamicin and they're like, 'Oh, no. They're resistant.' They're like, 'Oh, I'm going to give them these five other options first before I would even give them gent anyway, IV.' So we haven't really run across that, oh, we're stuck, we don't have anything and now we don't have [gentamicin], oh no.

Both SMEs who specialized in urology had used gentamicin bladder instillations as treatment for UTIs caused by multidrug resistant organisms. In patients with these UTIs, bladder instillation with gentamicin

solution was prescribed twice a day for 7 days. The SMEs commented that this treatment protocol was preferrable to intramuscular gentamicin administered twice a day in an office or hospital setting.

Neither of the SMEs who specialized in urology had patients who had experienced significant adverse effects from gentamicin bladder instillations. One SME remarked that studies of gentamicin bladder instillation in patients with non-neurogenic bladders had shown no systemic absorption of gentamicin. The SMEs did not routinely check serum gentamicin levels in patients on preventative bladder instillation therapy. One SME had done random serum gentamicin testing in patients on bladder instillations for a while, "[b]ut I got so many zero results that I also stopped doing it." The other SME occasionally evaluated serum gentamicin levels in response to patient or caregiver concerns, but not because of personal concern. This SME observed:

> I have certainly come across patients who worry when they look things up or read package inserts. And so, they have those concerns. And so, there've been . . . very occasional time[s] when particularly I'll see adult children with congenital problems. And so sometimes they're accompanied by parents, very frequently. And so, parents of adult children who've been medically complex their entire life are very hesitant and they see what gentamicin—the drug information is. And they say, 'No way I'm putting [it] into my child's bladder.' And so we'll draw a serum level, just a peak or a trough here or there just to prove to ourselves that they're not having absorption, but that's the furthest I've ever really taken that.

One SME noted that some patients cannot tolerate the cold/room temperature irrigant solution in their bladder. This SME stated:

> And it's actually called a cold water test. It's actually a urodynamic phenomenon that has been investigated and we know exists, it's just some people, you can't put something room temperature in their bladder. It spasms, and so that's . . . [y]ou don't know unless you try, but that's not that common, actually. Again, because it's a small volume. I mean, it's two tablespoons. So, it's not very much . . . but if you have a Foley already in, that might be your bladder capacity. So, rarely, someone can't tolerate it for that reason. But not really many other downsides.

In the SMEs' experience, patients elected to discontinue gentamicin bladder instillation therapy due to inability to tolerate cold solution, lack of dexterity necessary to self-administer the instillation solution, additional caregiver burden, and difficulty obtaining the solution and/or cost. One SME noted that purchasing the compounded gentamicin instillation solution can be very expensive for patients, depending on their insurance coverage and how the solution is dispensed. However, the SME observed:

> So, it all depends. And again, all people have a different threshold for what they consider value. There are people that have to pay out of pocket for gentamicin because it's not FDA-approved, and there are many people that say, 'Well, if I'm not going to end up in the ER all year, we're cost-neutral already.' And other people don't do the math as well in their head, and won't. . . . I've had people who get the gentamicin covered, but they have to pay out of pocket for saline, which is $2.50 a jug that will last a week. And they're not willing to invest that in their care. So people have different perspectives on what their health care is worth.

Regarding cost, the other SME remarked, "I've had a few patients who've come back with concerns about that, but I'll be honest with you, so many of these patients are so desperate that it's either a 911 call, an ambulance ride, an ER visit, admission to the hospital, IV antibiotics at home, or this. . . . I think there are some people who just would rather pay for this."

Both of the SMEs who specialized in urology worked at hospitals with on-site pharmacies that compounded the gentamicin instillation solution for individual patients. The solution was dispensed either

in person, for those patients who lived near the hospital, or shipped to their home. One SME stated that at their facility, the gentamicin instillation solution was available as a standard prescription in their electronic health record system. For patients who cannot obtain the gentamicin instillation solution from the on-site hospital pharmacy, one SME said that staff contact local compounding pharmacies and ask if they are capable of making and dispensing the solution. The other SME also had patients who utilized other pharmacies to obtain the gentamicin instillation solution, including outpatient pharmacies at community hospitals, local retail pharmacies, and compounding pharmacies. This SME said that finding a facility that was willing and able to compound and dispense the instillation solution was "pretty hit or miss" and "we've had a lot of patients get those prescriptions [paper prescriptions] rejected from every local option, and they end up with us as mail order patients."

The gentamicin instillation solution was dispensed in a variety of ways. One SME said that how the solution was dispensed depended on the facility from which the solution was obtained and the physical and mental capabilities and lifestyle of the patient. The SMEs had patients who utilized premixed syringes or mini-bags as well as patients who compounded the solution on their own at home using vials of gentamicin and saline bottles or bags. This SME observed that self-compounding and self-administration were difficult for patients with spinal cord injury or other compromise and introduced the potential for error. This SME shared:

> I know people in the peds world, in the pediatrics world, have given patients a recipe how to make their own saline. Saline, how to boil it and make sterile saline, and ask them to bring their saline in, and check their saline. And no one got it right. This is measuring water and salt and boiling it, and people can't do that. So, you have to be realistic. There are people that can do it, but, I mean, someone who only has one hand and one eye, and a tremor? It's really rough. So, I have people who don't do [gentamicin] washes because they can't get it pre-compounded . . .

This SME also noted that making and shipping premixed syringes was more expensive than dispensing vials of gentamicin and bags of saline for the patient to compound the solution at home. When asked how they would prefer that the gentamicin instillation solution to be dispense, one SME said, "I think if it were FDA-approved . . . [w]e'll talk about the ideal world. FDA-approved, available at pharmacies nationwide. I would much rather prescribe an off-the-shelf, single-dose little vial with a screw top or something you could go crack and put it in your catheter." The other SME thought that premixed syringes worked well for patients with limited dexterity or who were otherwise compromised because they eliminated the anxiety of having to draw up the solution from a bag or bottle.

Neither of the SMEs who specialized in urology had utilized gentamicin in combination with neomycin and polymyxin B as a bladder instillation solution. One SME did not see the utility of combining gentamicin with other antibiotics in a bladder instillation solution, commenting:

> The gentamicin concentration we use is super physiologic. I mean, giving it IV or IM never achieves that concentration in the urine, so even drug-resistant bugs, so bacteria that are gentamicin-resistant, I mean, that's . . . [g]entamicin-resistant is assessed at physiologic dose, not at the dose that we're giving. So, the concentration in the irrigant we're using just kind of gets pretty much everything. Not that they can't get UTIs, but we don't have the gentamicin in their bladder all the time, and people miss doses, and people go on vacation and that sort of thing. So, it's not foolproof, but I just don't see the purpose in mixing other antibiotics, because I'm not quite sure what you'd gain, and it sounds really complicated to make that.

This SME was not familiar with the safety of polymyxin B in the bladder, or the risk of systemic absorption, and therefore would not currently recommend its use in intravesical instillation solutions.

However, the SME did remark that if gentamicin was available in combination with other antibiotics as a sterile, off-the-shelf solution for bladder instillation, then they would use it because obtaining compounded gentamicin solution for bladder instillation is complicated and time-consuming for the nurse to coordinate. The SME stated, "So, if something was available off the shelf, sure. But if someone asks me, as a medical professional, do I think we need all those things? No, I don't think we need all those other things in there, because . . . I don't think you need to throw everything in there." The other SME concurred with these remarks, saying:

> And I will say that if it were commercially available to use it with multiple agents, I don't think I would be opposed to that. I just haven't had any experience with the agents. As much as patients have a million allergies, especially when we get to the point of refractory, recurrent infections, single-agent to me, seems like it makes more sense, because there's going to be less reactions. I've never had a clinical reaction of somebody with gentamicin.

This SME had used gentamicin in combination with other APIs as a bladder instillation solution in patients with interstitial cystitis. These patients received office-based bladder instillations with a "cocktail" once a week for 6 weeks. The SME stated that the cocktails varied, but often contained dimethyl sulfoxide (DMSO), "an old medicine that makes you smell like garlic and people don't love it." At the SME's practice, they used a cocktail with heparin, lidocaine, Solu-Medrol® (methylprednisolone sodium succinate), and bicarbonate, with or without gentamicin. This cocktail was instilled into the bladder in the clinic, allowed to dwell for 60 minutes and then the patient was allowed to urinate.

When asked for concluding statements regarding the use of gentamicin bladder instillation solutions, one SME said:

> I mean the reason I'm a champion for it, and I advocate for and prescribe it, is because I have people whose lives are completely different. I have people crying in my office because they're so happy. I have people send me portal messages about how they have a new life because of this. So, it's really. . . . There's not many things in this world that I get a massive thank you for. . . . And it's the same with gentamicin, people call and they're so upset that they're going to miss one dose. 'I need my prescription now, and you need to fax it now, because if I miss one dose, I'm terrified of that.' . . . I have people where it's completely changed their life, and . . . other than being inconvenient, there's very little loss. So, that's why I persevere, because I think if you took all these people's gentamicin, there'd be a revolt in my clinic, because so many people use it and they're so happy with it.

The other SME who specialized in urology hypothesized that the availability of a gentamicin bladder instillation solution would help community providers, both physicians and pharmacists, understand that it is an accepted therapy. Currently, a patient with a prescription for gentamicin bladder instillation solution might encounter rejection and/or questions at multiple pharmacies, which, according to the SME, makes these patients lose trust in the medical community. The availability of a gentamicin instillation solution would improve access for patients and legitimize the therapy among community providers and patients. Both SMEs agreed that gentamicin bladder instillation was a well-accepted therapy within the specialty of urology.

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 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain 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 5-minute gown and glove. If we don't have somebody in the IV room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 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 was focused on the utilization 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 utilization 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, as noted by 1 participant who stated 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 expressed 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 1 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. 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 [more] 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 was 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 room 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 utilized. However, the products utilized 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 9 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 continued 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 pre-shortage, you're not going to get products when you need it during the shortage," continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an 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 API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allow." 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 API 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 API. Another participant stated that as more outsourcing facilities began using API, 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 API if there is a shortage, stating, "I think the FDA has really looked closely at API, 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 from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic

products; however, 1 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 are 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 continued that while the evidence does not support many of the ingredients used in topical pain products, "However, 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 1 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 are 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 noted that it "is a challenge for anybody who has . . . 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 . . . 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 3 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 1 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 to [*sic*] 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 utilizing 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 . . . [i]t 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 quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented, "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 and 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 utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration 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, 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

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize 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 16).

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 17 for the categories of products obtained from outsourcing facilities.

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained gentamicin from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which gentamicin prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded gentamicin

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded gentamicin

No respondents to survey distributed via professional medical associations

Table 15. 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

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. 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

[a]Respondents allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. 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

[a]Respondents allowed to select multiple categories.
[b]Respondents 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 18. 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

[a]Respondents were allowed to select multiple products.

CONCLUSION

Gentamicin sulfate was nominated for inclusion on the 503B Bulks List as a 10-80 mg/100 mL irrigation solution, in combination with neomycin and polymyxin B for treatment of bladder infection, and as 10 mg/mL or 40 mg/mL intravenous and intramuscular solution for treatment of bacterial infections. Gentamicin sulfate is available as an FDA-approved injectable solution. Gentamicin is also available as an injectable solution in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and the UK. Gentamicin was not available in combination with neomycin and polymyxin B as a bladder instillation solution in any of the national medicine registers that were searched.

A literature review was not conducted for intravenous or intramuscular administration due to the availability of FDA-approved injectable gentamicin products. No studies were included from the literature review for a gentamicin/neomycin/polymyxin B bladder irrigation/instillation solution. However, several studies were identified in which gentamicin was used as a single-agent bladder instillation solution for prevention or treatment of recurrent UTIs. A few studies from the 1960s and 1970s were identified in which neomycin and/or polymyxin B were used as a bladder irrigation solution. The two SMEs who specialized in urology confirmed the findings from the literature that gentamicin instillation was an accepted therapy for the management of recurrent UTIs.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the prequestionnaire, 0 respondents obtained gentamicin from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to August 28, 2020
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 362

1	gentamicins/	18309
2	gentam#cin$.tw.	27401
3	or/1-2	32939
4	administration, intravesical/	3994
5	instillation, drug/	1454
6	therapeutic irrigation/	17473
7	lavage$.tw.	50472
8	instill$.tw.	27649
9	irrigat$.tw.	33802
10	intravesical$.tw.	9740
11	intra vesical$.tw.	124
12	or/4-11	122161
13	exp surgical procedures, operative/	3150287
14	exp infections/	2616808
15	antibiotic prophylaxis/	13959
16	ad.fs.	1417133
17	de.fs.	2992723
18	dt.fs.	2230036
19	tu.fs.	2228819
20	pc.fs.	1290187

21	su.fs.	1988790
22	surg$.tw.	1926046
23	perioperat$.tw.	96986
24	peri operat$.tw.	7246
25	intraoperat$.tw.	136236
26	intra operat$.tw.	15248
27	postoperat$.tw.	538286
28	post operat$.tw.	73348
29	preoperat$.tw.	293760
30	pre operat$.tw.	33323
31	infect$.tw.	1750278
32	prevent$.tw.	1427059
33	prophyla$.tw.	165367
34	neomycin/	7584
35	polymyxin b/	3251
36	neom#cin$.tw.	9620
37	polym#xin$.tw.	7822
38	polym#cin$.tw.	24
39	or/13-38	12552913
40	and/3,12,39	557
41	exp animals/ not humans/	4729286
42	40 not 41	441
43	limit 42 to english language	362

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 799

1	‘gentamicin’/de	109551
2	‘gentamicin*’:ti,ab,tn	32288
3	‘gentamycin*’:ti,ab,tn	4695
4	#1 OR #2 OR #3	114403
5	‘intravesical drug administration’/de	2740
6	‘lavage’/de	17386
7	‘bladder irrigation’/de	2367
8	‘drug instillation’/de	1824
9	‘lavage*’:ti,ab	73148
10	‘instill*’:ti,ab	40917
11	‘intravesical*’:ti,ab	14810
12	‘intra vesical*’:ti,ab	287
13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	131987
14	‘surgery’/exp	5370820
15	‘infection’/exp	3926701
16	‘antibiotic prophylaxis’/de	31840
17	‘infection prevention’/de	62321
18	‘drug administration’:lnk	1757254
19	‘drug therapy’:lnk	3929231
20	‘prevention’:lnk	1178117
21	‘surgery’:lnk	2181957
22	‘surg*’:ti,ab	2792163

23	‘perioperat*’:ti,ab	153767
24	‘peri operat*’:ti,ab	15712
25	‘intraoperat*’:ti,ab	215093
26	‘intra operat*’:ti,ab	29204
27	‘postoperat*’:ti,ab	858349
28	‘post operat*’:ti,ab	152638
29	‘preoperat*’:ti,ab	468982
30	‘pre operat*’:ti,ab	68090
31	‘infect*’:ti,ab	2347503
32	‘prevent*’:ti,ab	1937390
33	‘prophyl*’:ti,ab	263945
34	‘neomycin’/de	25393
35	‘polymyxin b’/de	11064
36	‘neomicin*’:ti,ab,tn	27
37	‘neomycin*’:ti,ab,tn	12382
38	‘polymixin*’:ti,ab,tn	533
39	‘polymyxin*’:ti,ab,tn	9524
40	‘polymicin*’:ti,ab,tn	1
41	‘polymycin*’:ti,ab,tn	58
42	#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 OR #37 OR #38 OR #39 OR #40 OR #41	14034430
43	#4 AND #13 AND #42	1074
44	[animals]/lim NOT [humans]/lim	6081128
45	#43 NOT #44	919
46	#43 NOT #44 AND [english]/lim	799

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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer gentamicin sulfate / neomycin / polymyxin B to your patients?
    - Yes
    - No
3. Do you prescribe or administer gentamicin sulfate / neomycin / polymyxin B by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Bladder irrigation/instillation solution
    - None of the above
4. I prescribe or administer gentamicin sulfate / neomycin / polymyxin B for the following conditions or diseases: (check all that apply)
    - Urinary tract infection
    - Other (please explain) _____
5. I use compounded gentamicin sulfate / neomycin / polymyxin B 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 gentamicin sulfate / neomycin / polymyxin B
    - Other (please explain) _____
6. Do you stock non-patient-specific compounded gentamicin sulfate / neomycin / polymyxin B at your practice?
    - Yes
    - No
    - I'm not sure
7. I obtain compounded gentamicin sulfate / neomycin / polymyxin B 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) _____

8. 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) _____
9. 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 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

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.