

FDA Opening Remarks

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Antimicrobial Drugs Advisory Committee Meeting

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Introduction

- Discussion of the safety and efficacy of bacitracin for injection for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug
- Consideration of other uses that could be studied
- No discussion of topical and ophthalmic formulations of bacitracin

Bacitracin for Injection

- Polypeptide complex derived from cultures of *Bacillus subtilis* (Tracey); bacitracin A is major component
- Active in vitro against a variety of gram-positive and a few gram-negative organisms
- Assayed against a standard; activity expressed in units, with 1 mg having a potency of not less than 50 units
- Available as sterile powder in vials containing 50,000 units
- Marketed under several approved abbreviated new drug applications

Bacitracin for Injection

- Indications and Usage: Use is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug
- For intramuscular administration only; dissolved in sodium chloride for injection containing 2% procaine hydrochloride
- Dose
 - Under 2500 grams: 900 units/kg/day in 2 or 3 divided doses
 - Over 2500 grams: 1000 units/kg/day in 2 or 3 divided doses

Bacitracin for Injection

- Boxed Warning for nephrotoxicity
 - May cause renal failure due to tubular and glomerular necrosis
 - Monitor renal function, maintain proper fluid intake and urinary output, discontinue if renal toxicity occurs
- Warning for anaphylaxis and/or allergic contact dermatitis when used for non-approved indications
- Adverse Reactions
 - Nephrotoxic: albuminuria, cylindruria, azotemia; rising blood levels without any increase in dosage
 - Other: nausea, vomiting, pain at injection site, rashes

Regulatory History

- 1948: Upjohn Company application for bacitracin sterile powder, 10,000 and 50,000 units per vial, became effective
- 1950: Charles Pfizer & Company application for bacitracin sterile powder, 50,000 units per vial, became effective
- 1962: Congress amended the Food, Drug, and Cosmetic Act (FD&C) to require that new drugs be proven effective, as well as safe, to obtain FDA approval; FDA required to conduct retrospective evaluations of effectiveness of drug products approved as safe between 1938 and 1962

Drug Efficacy Study Implementation

- FDA contracted with National Academy of Sciences/National Research Council (NAS/NRC) to make initial evaluation of effectiveness of products approved only for safety between 1938 and 1962
- NAS/NRC created review panels; reports submitted to FDA in late 1960s and early 1970s
- FDA reviewed and re-evaluated the panel findings and published its findings in *Federal Register* notices
- Administrative implementation of NAS/NRC reports was called Drug Efficacy Study Implementation (DESI)

Bacitracin for Injection DESI Review

- Pre-DESI indications reviewed by NAS/NRC Panel on Anti-Infective Drugs
 - Intramuscular injection in the treatment of infections caused by bacitracin-sensitive organisms resistant to penicillin and other antibiotics
 - Local injection into circumscribed areas such as furuncles, carbuncles, or abscesses
 - In conjunction with intramuscular administration, has been used successfully by intrathecal, intraventricular, intracisternal, or intracerebral injection in the treatment of neurosurgical infections, including osteomyelitis of the skull, septic coccal meningitis, brain abscess, and postoperative infections
 - Locally by topical application in the treatment of susceptible infections of skin, eye, nose, throat; surgical infections of soft tissue and bone; prophylaxis in burns

Bacitracin for Injection DESI Review

- 1970 DESI notice for bacitracin drug products
 - “Probably effective”
 - Intramuscularly for treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug; topically (in solution) for superficial infections caused by susceptible organisms
 - Notice stated that applicants had 12 months to obtain and submit data to provide substantial evidence of effectiveness
 - “Possibly effective”
 - In conjunction with intramuscular administration for susceptible nonsurgical or neurosurgical infections; topically for treatment skin, eye, nose, throat infections; in compresses or instillations for secondarily infected wounds, ulcers, and pyodermas
 - Notice stated that applicants had 6 months to obtain and submit data to provide substantial evidence of effectiveness

Amended DESI Notice

- 1972 amended DESI notice for bacitracin sterile powder
 - “Effective” intramuscularly for treatment of infants with pneumonia and empyema caused by staphylococci
 - Letter from NAS/NRC Panel on Anti-Infective Drugs chair: “We have used it in two such instances in the past year and, as might be expected, the drug performed quite well. No other medication presently available would have fulfilled this role since vancomycin is too toxic for use in small children.”
 - Other indications found to be “probably effective” and “possibly effective” reclassified as lacking substantial evidence of effectiveness; no new evidence submitted

1984 Anti-Infective Drugs Advisory Committee

- Reassessment of risks and benefits of bacitracin for injection for treatment of infants with pneumonia and empyema
- Recommended withdrawal of bacitracin for injection from certification because of an unfavorable risk-benefit assessment
- Committee noted significant risk of nephrotoxicity and availability of alternative drugs for the treatment of staphylococcal pneumonia in infants
- None of five committee members believed that bacitracin for injection was safe and effective for the approved indication

Current Status of Bacitracin for Injection

- Following 1984 advisory committee meeting, bacitracin for intramuscular injection remained on the market with the current, sole approved indication: treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug
- Substantial use for unapproved indications, primarily in surgical settings

Outline for the Session

- FDA presentation
- Industry presentation
- Open public hearing
- Questions to the committee

Questions

1. Do the benefits of bacitracin for intramuscular injection outweigh the risks for its approved indication of the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug?
 - If yes, please provide any recommendations concerning labeling.
 - If no, please provide your rationale.
 - Please provide any additional comments or thoughts on your vote.
2. Are there uses for bacitracin for intramuscular injection other than for treatment of infants with pneumonia and empyema caused by staphylococci that could be studied?



U.S. FOOD & DRUG
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BACITRACIN FOR INTRAMUSCULAR INJECTION

LABELED INDICATION AND CURRENT USES

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Presentation Outline

- Bacitracin for injection for treatment of pneumonia in infants
 - Literature summary
- Current uses of bacitracin for injection
 - Utilization data
 - Safety analyses

Bacitracin

- Bacitracin is a mixture of peptides which acts by interfering with bacterial cell wall synthesis. The drug is active against gram-positive organisms including *Staphylococcus aureus* and *Streptococcus species*.
- Only labeled indication: “Limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to bacitracin”*
- Labeling includes a boxed warning stating that the drug may cause renal failure due to tubular and glomerular necrosis.
- FDA-approved antibacterial drugs for the treatment of staphylococcal pneumonia in infants include anti-staphylococcal penicillins (e.g., oxacillin), first-generation cephalosporins (e.g., cefazolin), vancomycin, linezolid, and clindamycin.

Bacitracin for Treatment of Pneumonia in Infants



- Literature review for use of bacitracin in infants with staphylococcal pneumonia was performed.
- A total of 4 articles published between 1957 and 1972 were identified.
- No relevant publications were identified after 1972.
- All 4 publications provided very limited information on use of intramuscular bacitracin for treatment of staphylococcal pneumonia in infants.
- Bacitracin was administered intra-pleurally in neonates with empyema.

Literature Summary: Bacitracin for Treatment of Pneumonia in Infants

- Koch et al. (1957): Retrospective, single center case series of various staphylococcal infections in children aged 2 days to 15 years. The number of children with staphylococcal pneumonia treated with bacitracin and their clinical outcomes was not described.
- Pryles et al. (1958): Bacitracin was instilled in intrapleural space without adverse outcomes. Recommended local administration in severely ill infants with massive empyemas, while exercising “considerable caution”, in addition to systemic therapy. No nephrotoxicity observed (n=7 patients).

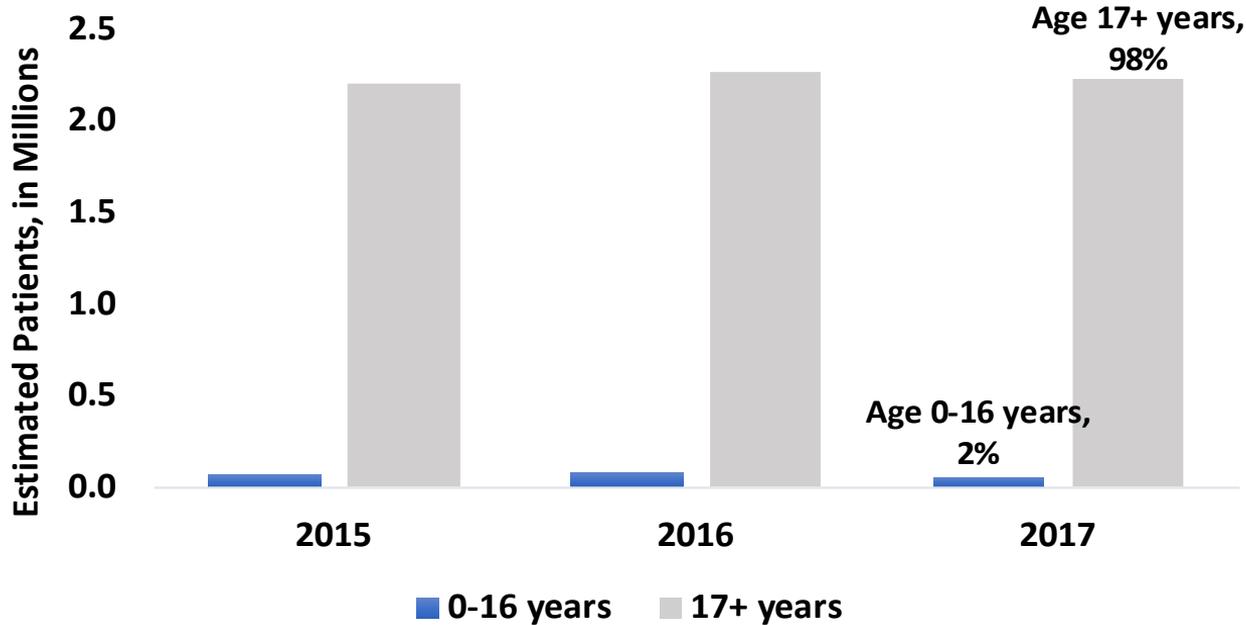
Literature Summary: Bacitracin for Treatment of Pneumonia in Infants

- Gourlay et al. (1962) Retrospective, single center case series of staphylococcal pneumonia and empyema. The number of children treated with bacitracin and their clinical outcomes not described. Bacitracin intramuscular injection described as a recommended therapy in “desperately ill” patients; however, with arrival of newer antibiotics “kanamycin and vancomycin were administered in preference.”
- Geley et al. (1972) Series of 273 cases from 1954-1956 and 1957-1970, 152 with *S. aureus*. A singular reference is made to bacitracin, used in combination with neomycin, as “excellent local antibiotics” for instillation into the pleural cavity in neonates and infants with empyema. Unclear how many children in this case series received this drug combination as well as clinical, efficacy, or microbiologic outcomes of intervention in response to combination therapy.

Bacitracin Current Uses

- Analyses of bacitracin utilization data and review of the literature suggest that bacitracin for injection is currently administered mainly for unapproved uses.
- Primary usage is in the operating room.

Bacitracin Current Use (by Patient Age)



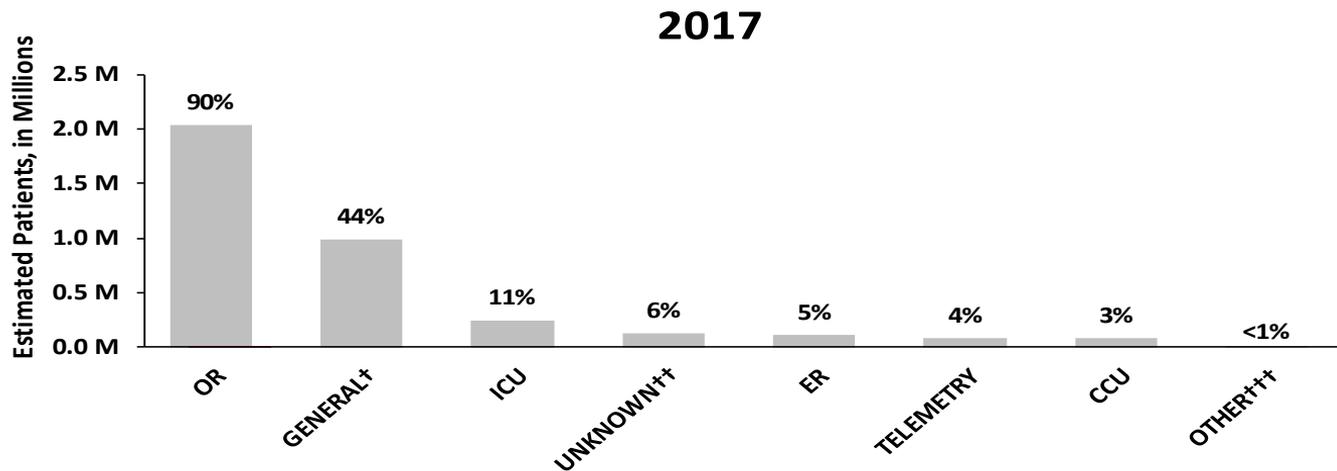
Nationally estimated number of patients with a hospital discharge billing for bacitracin injection, stratified by patient age, from U.S. non-federal hospitals*

Source: IQVIA, Hospital Visit Analyzer (HVA). 2015-2017. Data extracted December 2018.

*Database does not include standalone children’s hospitals and other specialty hospitals

Bacitracin Current Use (by Location of Care)

Majority of Use was in the Operating Room



Estimated number of patients discharged from U.S. non-federal hospitals and billed for bacitracin injection, stratified by location of care in 2017

Source: IQVIA, Hospital Visit Analyzer (HVA). Year 2017. Data Extracted January 2019.

Note: Location is the area in the hospital where the patient was on the day of treatment. Because patients can receive injectable bacitracin in multiple locations on the same day or across multiple days during the same inpatient visit, the sum of patients or hospital visits across locations is higher than the total unique patients. The total percentage of patients across locations is more than 100%.

† General unit or general floor is described as a private or semi-private hospital room or bed; ††Unknown means the categories for blank entries in the claim

††† Other means grouping of locations with very few entries; CCU = coronary care unit, ER = emergency room, ICU = intensive care unit, OR = operating room

Bacitracin Current Uses: Literature Review

- Existing literature comprised mostly of retrospective, observational, single-center studies, reporting on off-label uses of bacitracin for injection.
- Most commonly identified use of bacitracin for injection is as a component of intraoperative irrigation solutions, for example:
 - In plastic surgery in combination with other antibacterial drugs (during breast reconstruction procedures)
 - In orthopedic surgery (irrigation, debridement of prosthetic joint infections)
 - In cardiac surgery (implantable electronic devices)
- It appears that the practice patterns of bacitracin usage vary considerably between institutions.

Topical Antimicrobials for Prevention of Surgical Site Infection (SSI)

- **Joint clinical practice guideline*** states that there is no additional benefit of topically administered antimicrobial irrigation solutions, pastes, or washes when used as adjuncts to parenteral antimicrobial prophylaxis, and that additional data are needed to support this practice
- **American College of Surgeons and Surgical Infection Society** state that there is insufficient evidence to recommend routine use of topical antimicrobial therapy to decrease the risk of SSI
- **Centers for Disease Control and Prevention** guideline for the prevention of SSI states that there are uncertain trade-offs between the benefits and harms of intraoperative antimicrobial irrigation and that no recommendation could be made regarding its use

* American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of American (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA)

Bacitracin Safety Concerns

- Nephrotoxicity
 - Renal tubular and glomerular necrosis
 - Proteinuria
 - Decrease in renal function
- Hypersensitivity reactions, including anaphylaxis
 - Bacitracin cited as 8th most frequent allergen in North America among topically administered drugs*
- Medication errors where irrigation solutions were inadvertently administered intravenously

* Dermatitis. 2018 Nov/Dec; 29(6):297-309.

Nephrotoxicity

- Non-clinical Studies: Nephrotoxic in mouse, rat, and monkey studies
 - Mouse/rat: tubular degeneration and necrosis
 - Monkey: proteinuria and glycosuria
- Study in healthy volunteers showed occurrence of proteinuria, urinary casts, and reduction in renal function
- 270 patients who received 50,000 units of bacitracin every 6 hours administered locally or systemically; reported events include:
 - Albuminuria: Albumin appeared in urine 2 to 3 days after bacitracin treatment started;
 - Active urine sediment on urine microscopic analysis: urine casts
 - Uremia
 - Declines in glomerular and tubular filtration (GFR) and of specific gravity
- 148 patients with early syphilis received parenteral bacitracin
 - All 148 developed proteinuria and casts during course of therapy
 - Hematuria rare

Safety: Current Uses

- PubMed search for articles related to adverse events associated with use of bacitracin in irrigation solutions or in context of surgical procedures
- Retrieved 12 relevant citations published between 1979 and 2017
 - 10 were case reports involving 12 patients*
- Of the 12 cases:
 - 11 cases reported anaphylactic reactions (9 following bacitracin irrigation, 1 medical device soaked in bacitracin, 1 bacitracin soaked gauze applied to surgical cavity)
 - 1 case of mediastinal irrigation resulting in increase in serum bacitracin levels and increase in serum BUN (serum Cr and urine output remained normal)

*6 citations were included in the FAERS database

Safety: FDA FAERS Database*

- FAERS reports through December 12, 2018
 - Included reports of parenteral routes of administration, e.g., intramuscular, intravenous, intraperitoneal, etc.
- Identified 35 cases: 24 bacitracin irrigation cases, 11 intravenous cases
 - Most cases in persons 17 years of age and older
 - Most frequently reported MedDRA[†] preferred terms (PT) for irrigations: hypersensitivity (10), dermatitis (9), application site reaction (8), anaphylactic reaction (4), anaphylactoid reaction (3), hypotension (3)
 - Most frequently reported MedDRA PTs for intravenous route: accidental overdose, headache, medication error, photophobia, pyrexia (2 cases for each preferred term)

*FDA Adverse Event Reporting System; [†]Medical Dictionary for Regulatory Activities

Summary

- Review of the literature identified very limited information on use of bacitracin for injection in infants with staphylococcal pneumonia
- There are several approved antibacterial drugs for the treatment of infants with staphylococcal pneumonia
- Use of intramuscular bacitracin for injection is not consistent with treatment guidelines or clinical practice for the treatment of staphylococcal pneumonia in infants
- The current uses of bacitracin for injection appears to be primarily in adults in the operating room
- Hypersensitivity reactions, including anaphylaxis and nephrotoxicity are the most commonly reported adverse reactions
- Findings of nephrotoxicity including proteinuria, urinary casts, and reduced renal function have been reported with systemic and topical use



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