Administration of Ceftobiprole medocaril

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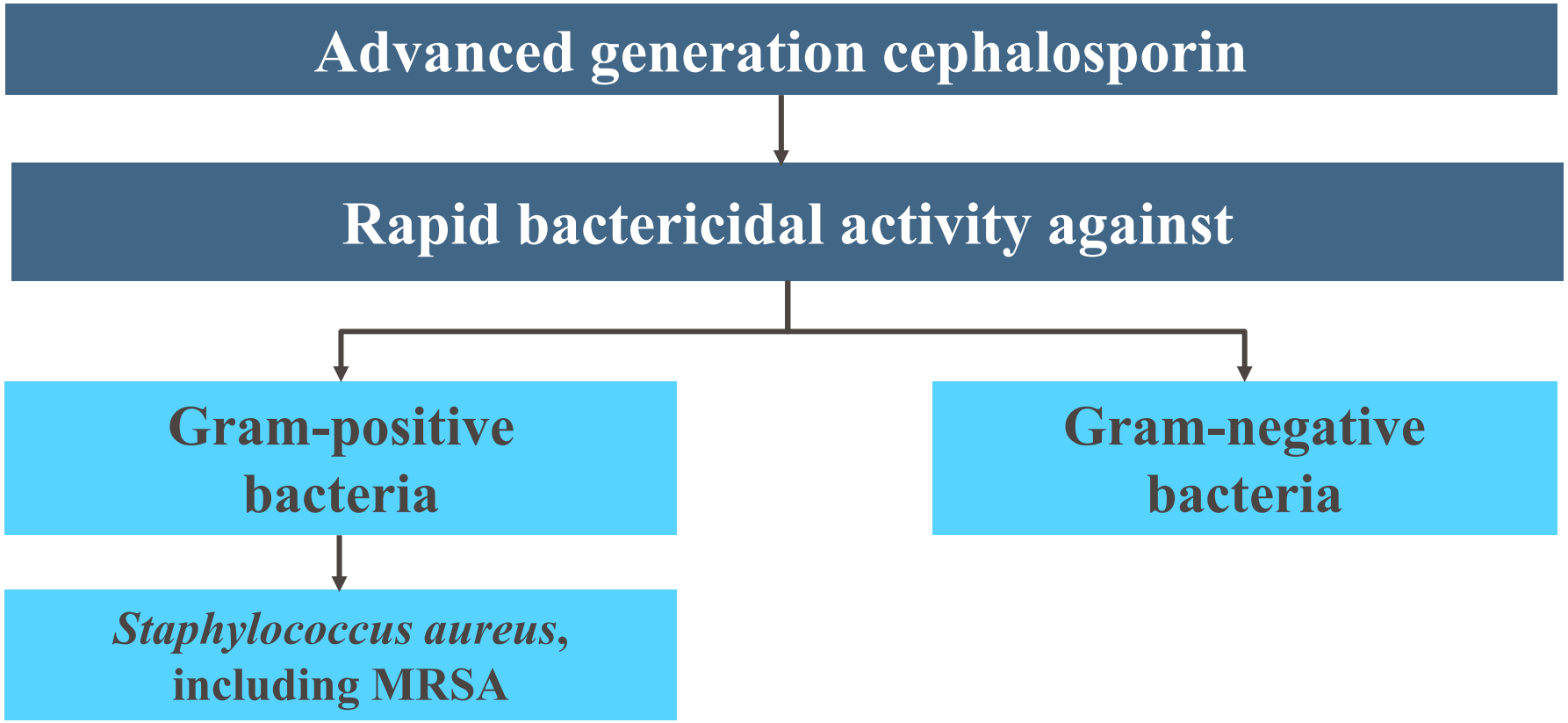
Threat of Antibiotic-Resistant Organisms Growing Faster than Development of Treatments

- Antibiotic resistance poses major threat to human health
- Infections caused by antibiotic-resistant organisms, including MRSA, increase morbidity and mortality and increase hospital burden
- CDC estimates 2 million patients/year have infections due to drug-resistant bacteria[1]
  - Resulting in 23,000 deaths annually in US
- MRSA substantial portion of burden
  - Classified as serious threat by CDC and considered high-priority pathogen in urgent need of new options
- > 100,000 deaths and loss of 3.5 million disability-adjusted life-years attributable to resistance[2]

1. CDC.gov; 2. Murray et al. 2022

About Ceftobiprole



Safety consistent with cephalosporin class

MRSA: methicillin-resistant *Staphylococcus aureus*

Ceftobiprole Mechanism of Action

- Ceftobiprole medocaril is water-soluble prodrug

- Exerts bactericidal activity through strong binding to penicillin-binding proteins, including PBP2a (MRSA)

- Activity has been extensively characterized in *in vitro* and *in vivo* efficacy models

- Low propensity for development of resistance

Ceftobiprole Nonclinical Safety Profile Is Similar to Other Cephalosporins

- Comprehensive nonclinical safety pharmacology program
- Well-established nonclinical safety profile similar to other β-lactams
- Nonclinical studies suggest low potential for adverse effects

Documentation of Administration

- Documentation of administration of ceftobiprole within the medical records would most commonly be found in the Medication Administration Record (MAR) and Electronic Health Records (EHR), progress reports and pharmacy records.

- Ceftobiprole administration should be documented consistent with the documentation associated with other intravenous injections of antimicrobials

Recommended dose

- *For community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI)*
  - Ceftobiprole is administered as a 500mg, 2-hour intravenous infusion three times a day (Q8h) for 5-14 days
- *For Staphylococcus aureus bacteremia (SAB) including cases of infective endocarditis*
  - Ceftobiprole is administered as a 500mg, 2-hour intravenous infusion four times daily (Q6h) for the first 8 days, followed by a three times daily infusion for the subsequent days up to a total of 42 days.

Ceftobiprole Consistently Demonstrated Non-Inferiority Against SoC Across All Prespecified Endpoints

SAB

- N = 390 adults
- Randomized, double-blind, non-inferiority, active-controlled study for patients with bacteremia and evidence caused by *S. aureus*

Ceftobiprole vs daptomycin +/- aztreonam

ABSSSI

- N = 679 adults
- Randomized, double-blind, non-inferiority, active-controlled study for patients with qualifying ABSSSI and required IV antibiotics

Ceftobiprole vs vancomycin + aztreonam

CABP

- N = 638 adults
- Randomized, double-blind, non-inferiority, active-controlled study for patients hospitalized with CABP in need of IV antibiotics

Ceftobiprole vs ceftriaxone +/- linezolid

Peds

- N = 138 patients 3 m to < 18 y
- Randomized, double-blind, non-inferiority, active-controlled study for patients hospitalized with CABP and HABP in need of IV antibiotics

Ceftobiprole vs cephalosporin +/- vancomycin

Ceftobiprole Proposed Indications

Staphylococcus aureus bacteremia (SAB)

Treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia), **including those with right-sided infective endocarditis (RIE),** caused by methicillin-susceptible and methicillin-resistant isolates.

Acute bacterial skin and skin structure infections (ABSSSI)

Treatment of adult patients with acute bacterial skin and skin structure infections caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (methicillin susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Escherichia coli*, and *Klebsiella pneumoniae*.

Community-acquired bacterial pneumonia (CABP)

Treatment of adult and pediatric patients (≥ 3 months of age) with community-acquired bacterial pneumonia caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Haemophilus parainfluenzae*.

Safety Exposures: > 800 Patients Exposed to Ceftobiprole in Phase 3 Studies

Population	Ceftobiprole N = 835	Comparator N = 862
Duration (days), **mean** (SD)		
SAB	**21** (7.5)	**21** (6.7)
ABSSSI	**7** (2.4)	**7** (2.7)
CABP	**9** (2.9)	**9** (2.7)

Pooling of clinical study safety data agreed with FDA

Overall Pooled Safety

	Ceftobiprole N = 835	Comparator N = 862
Any AE	58.2%	53.0%
Study drug-related AE	24.2%	18.1%
Severe AE	7.8%	10.6%
SAE	9.2%	10.9%
AE leading to dose adjustment or interruption	2.0%	0.8%
AE leading to treatment discontinuation	5.0%	4.6%
Death	27 (3.2%)	29 (3.4%)

Pooled Safety: Proportion of Patients Who Experienced ≥ 1 AE Similar Between Groups

Occurring in ≥ 5% in either group	Ceftobiprole N = 835	Comparator N = 862
Any AE	**58.2%**	**53.0%**
Nausea	**10.3%**	**4.8%**
Diarrhea	**6.7%**	**5.7%**
Vomiting	**6.0%**	**2.3%**
Headache	**5.4%**	**6.1%**

Summary

1. Ceftobiprole has demonstrated efficacy in three indications for the treatment of serious bacterial infections, often caused by resistant bacteria

2. > 800 patients treated with ceftobiprole in adult Phase 3 studies in SAB, ABSSSI and CABP; 94 pediatric patients with pneumonia

3. Safety profile further supported by 18 Phase 1 studies and post marketing surveillance data outside of US over 10 years