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Is Ceftobiprole a Safe and Effective Treatment for Skin and Skin Structure Infections?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not ceftobiprole is a safe and effective treatment for complicated skin and skin structure infections

STUDY DESIGN: Review of all English language primary randomized controlled trials from 1996-2010

DATA SOURCES: Three randomized controlled trials were found using Pubmed and Cochrane databases

OUTCOMES MEASURES: Skin or skin-structure infection cure with ceftobiprole intervention and adverse effects of this new pharmaceutical. Cure or failure to cure skin infection was determined based on both clinical and microbiological assessment. Adverse events were measured based on patient reports, clinician reports, labs, and vital sign assessment.

RESULTS: Noel, Strauss et al. found statistically significant cure rates of complicated skin and skin-structure infections with intervention of ceftobiprole compared to the standard control arm. Noel, Bush et al. found similar results when comparing ceftobiprole with the control arm. Both studies concluded that ceftobiprole was non-inferior to the leading treatment for complicated skin infections, and caused complete microbiological and clinical resolution of complicated skin infections. Schmitt-Hoffmann et al. concluded that ceftobiprole was safe for human consumption with no severe adverse effects noted.

CONCLUSIONS: Cefrobiprole is comparable to vancomycin in both safety and effectiveness for treatment for skin and skin-structure infections

KEY WORDS: Ceftobiprole, Skin infections; Skin structure infections, BAL5788

INTRODUCTION

An uncomplicated skin infection is the colonization of epidermal and dermal tissue with a parasitic pathogen. Complicated skin infections, as defined by Noel, Strauss et al, involve the subcutaneous tissue or require significant surgical intervention and one or more of the following: a wound infection, an abscess, or cellulitis.[1] The most common pathogens causing skin and skin-structure infections include *Streptococcus pyogens*, *Staphylococcus aureus*, and recently, an increase of methicillin-resistant *Staphylococcus aureus* (MRSA). Treatment of complicated skin and skin-structure infections typically begins with empiric broad-spectrum antibiotics such as vancomycin, which is then tailored to a more narrow spectrum antibiotic based on sensitivity results. This review evaluates three randomized controlled trials that compare ceftobiprole, a novel antibiotic, to standard treatment with vancomycin for the treatment of complicated skin and skin-structure infections.

Ceftobiprole is an investigational novel pyrrolidinone cephalosporin still in clinical trials and unavailable in the Unites States.[1] It is a broad-spectrum anti-MRSA antibiotic developed in 2004 by Basilea Pharmaceuticals and further developed and researched by Johnson and Johnson Pharmaceuticals. It shows activity against multiple pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), Enterobacteriaceae and *Pseudomonas aeruginosa*. The research articles used in this review studied the safety and efficacy of this novel antibiotic on complicated skin infections.

The diagnosis and treatment of complicated skin infections is within a physician assistant's scope of practice. Physician assistants are involved in care in multiple specialties that regularly treat patients with skin infections. Some of these include Dermatology, Family Medicine, Emergency Medicine, Pediatrics, Internal Medicine and Surgery. Because complicated skin infections occur commonly, physician assistants must stay abreast of changes and advancements in treatment options.

The incidence of complicated MRSA related skin infections is showing an upward trend. MRSA is now responsible for 60% of purulent skin and soft tissue infections in patients presenting to emergency rooms in the United States.[4] MRSA infections alone cost the healthcare system an estimated $830 million- $9.7 billion in 2005 alone and were responsible for 278,203 hospitalizations in 2005. [4,5]

In the coming years, physician assistants are expected to encounter multiple skin infections with MRSA as a main causative pathogen. According to Graham et al's population based survey, 95 million Americans carry S. aureus in their noses.[5] Of these, 2.5 million (2.6% of carriers) carry MRSA.[5] The incidence of complicated MRSA infections is also increasing over time. Between 1999 and 2005, the estimated number of S. aureus related hospitalizations increased 62%, from 294,570 to 477,927.[5] The number of serious complicated skin infections requiring hospitalizations is also increasing. Between 1999 to 2005, the estimated number of MRSA-related hospitalizations more than doubled, from 127,036 to 278,203.[5] For these reasons, physician assistants must be aware of all potential ways to treat complicated skin infections caused by an increasingly common MRSA pathogen.

Because MRSA has become an increasingly ubiquitous, physician assistants must consider the possibility of MRSA as a causative agent in all skin infections and treat accordingly with a broad spectrum antibiotic until further culture and sensitivity is available. Currently, the most commonly used medication to treat these infections is vancomycin. However, new evidence from Noel et al suggests that ceftobiprole may be an effective alternative to vancomycin in treating complicated skin infections.

Ceftobiprole was developed in an effort to create more new agents with reliable activity against MRSA. The trials selected by the author compare ceftobiprole to vancomycin, the current standard of care for the treatment of skin infections due to gram positive bacteria in which methicillin resistance is a significant concern.[1]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not ceftobiprole is a safe and effective treatment for complicated skin and skin-structure infections.

METHODS

Selected articles included adults 18 years of age and older with complicated skin and skin-structure infections. Interventions used varied by the study. Two studies examined the efficacy of ceftobiprole by comparing ceftobiprole with vancomycin or vancomycin plus ceftazidime and one study examined the safety of ceftobiprole. In the Noel, Bush et al. study, the intervention involved combining ceftobiprole plus placebo vs. vancomycin plus ceftazidine.[2] Noel, Stauss et al. intervene by giving vancomycin vs ceftobiprole.[1] Outcomes measured included cure of skin infection defined as "resolution of all signs and symptoms of the infection or improvement to such an extent that no further antimicrobial therapy was necessary," and presence of significant adverse events.[1] In Schmitt-Hoffman et al (2004), safety was assessed by giving participants either placebo BID, 500 mg ceftobiprole BID or 750 mg ceftobiprole BID.[3] The main focus of this study was to determine safety of the drug by assessing adverse events including serious adverse events.

Three randomized controlled studies were used for this systematic review. The author performed searches on Pubmed and Cochrane databases, using key words "ceftobiprole" and "BAL5788," and by limiting results to those written in English. Inclusion criteria consisted of articles published in peer-reviewed journals and were chosen based on outcomes significant to the patient. Articles were excluded if performed before 1996 or if participants were under age of 18. Both Noel et al. studies used confidence intervals (CI) to determine significance. The Schmitt-Hoffmann et al study, which examined the safety of ceftobiprole used number needed to harm (NNH) to assess adverse

effects of the drug at different doses versus a placebo. **Table 1** demonstrates the demographics used in the studies examined.

Table 1: Demographics of included studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Noel GJ, Bush K et al (2008) 1	RCT*	784	18-91	Adults 18 years or older who have a clinical diagnosis of complicated skin and skin structure infections caused by documented or suspected Gram-positive bacteria	Pts with allergic reactions to cephalosporins or vancomyocin, pregnant or lactating women, neutropenia, HIV infected with low CD4 count, diabetic foot infections, osteomyelitis, animal or human bites, recent antimicrobial treatment x >24 hours in last 7 days	118	Ceftobiprole 500 mg BID x 7-14 days or Vancomycin 1g BID x 7-14 days
Noel GJ, Strauss RS. et al (2008) 2	RCT	828	19-92	Adults 18 yrs or older diagnosed with skin or skin structure infection	Pts with foreign body infection, osteomyelitis, critical limb ischemia, septic arthritis	66	Ceftobiprole 500 mg infusion over 120 min q 8 hrs x 7-14 days + Placebo infusion over 60 min q 12 hrs x 7-14 days or Vancomycin 1 g infusion over 60 min q 12 hrs x 7-14 days + Cetazidine 1 g infusion over 120 min q 8 hrs x 7-14 days
Schmitt-Hoffman (2004) 3	RCT	16	19-38	>18 yrs Completed medical exam within normal limits	Completed medical exam outside of normal limits	0	Placebo BID x 8 days or Ceftobiprole 500 mg BID x 8 days or Ceftobiprole 750 mg BID x 8 days

RCT = Randomized Controlled Trial

OUTCOMES MEASURED

Outcomes measured in this review include efficacy of ceftobiprole and safety of ceftobiprole. Efficacy, in both Noel et al studies, was measured by categorizing outcomes dichotomously into either skin infection cure or failure.[1,2] Cure was defined as a complete resolution of all symptoms of the skin and skin-structure infection or improvement to such an extent that no further antimicrobial therapy was necessary.[1] Failure was defined as a need for further treatment with a non-study drug or discontinuation of the study drug after three days secondary to ineffectiveness.[1,2]

Efficacy outcomes were measured in a standardized way through both microbiological assessment and clinical assessment. Microbiological assessment was measured via gram stain and culture of the skin and skin-structure infection site.[1,2] The offending pathogen was identified in this way. At the end of treatment, a repeat gram stain and culture of infected are were taken. Negative gram stain and culture indicated cure of skin infection. Clinical outcomes were measured based on blinded clinician's assessment of the presence of signs and symptoms of skin infection.

Safety outcomes of ceftobiprole were measured by both Noel et al. studies and additionally by Schmitt-Hoffmann et al. Safety data was collected by Schmitt-Hoffmann et al. via blood samples for laboratory safety tests, vital signs and pt reported adverse events. An adverse event (AE) was defined as any adverse change that occurred after a patient was given a study drug. The Noel et al. studies mainly used patient reports for adverse reactions.

RESULTS

All results in the three analyzed studies utilized dichotomous data: skin infection cured or not cured, and adverse effect or no adverse effect. Inclusion criteria for all studies included patients 18 years of age or older. Both Noel et al. studies included only those who were diagnosed with a

complicated skin or skin structure infection. Cellulitis cases were limited to 20% of the final patient population.[1,2] Exclusion criteria included allergy or intolerability to cephalosporins or vancomycin, severe renal dysfunction, hepatic dysfunction, pregnant or lactating women, neutropenia, HIV with low CD4 counts, diabetic foot infections, animal or human bites, osteomyelitis, critical limb ischemia, septic arthritis, or systemic antibiotics for more than 24 hours in the last 7 days.[1,2]

Noel, Bush et al. reported a cure rate of 90.5% for the Ceftobiprole group and 90.2% for the group treated with vancomycin and ceftazidime which were proven to not be significantly different (95% CI, -4.4%, 3.9%).[2] The relative risk reduction (RRR) was 0.003 and the absolute risk reduction (ARR) was 0.3%. This study determined the number needed to treat (NNT) was 333 participants (**Table 2**).[2]

Noel, Strauss et al determined a cure rate of 93.3% of participants being treated with ceftobiprole and 93.5% cure rate for those taking vancomycin which were not significantly different (95% CI, -4.2%, -4.9%).[1] The relative risk reduction was 0.002 and the absolute risk reduction was found to be -0.2%. The number needed to treat for this study was -500 participants (**Table 2**).[1]

Table 2. Efficacy of Ceftobiprole vs Vancomycin on skin infections

	Ceftobiprole	Vancomycin	Vancomycin + ceftazidime	95% CI* of difference in cure rates	RBI*	ABI*	NNT*
Noel, Bush, et al (2008)	439/485 (90.5%)	N/A	220/244 (90.2%)	-4.4% - 3.9%	0.30%	0.30%	333
Noel, Strauss, et al (2008)	262/282 (93.3%)	259/277 (93.5%)	N/A	-4.2% - 4.9%	-0.20%	-0.20%	-500

*CI = Confidence Interval, RBI = Relative Benefit Increase, ARR = Absolute Benefit Increase, NNT = Number Needed to Treat

Ceftobiprole was found to be effective against a number of common gram-positive bacteria

according to both Noel et al. studies. Two organisms cultured and followed in both studies was methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA).[1,2] A summary of cure rates based on organism type can be found in **Table 3**. According to both studies, ceftobiprole was found to be non-inferior to vancomycin in treating both MSSA and MRSA infections.[1,2] Noel, Strauss et al. found ceftobiprole cured 91.8% of MRSA infections and vancomycin cured 90.0% of cases which was not significantly different (95% CI, -8.4%, 12.1%).[1] Noel, Bush et al also found no significant difference between ceftobiprole and vancomycin when treating MRSA.[2] This study reported 89.7% MRSA cure rate for ceftobiprole and 86.1% cure rate of MRSA in the vancomycin group which is not significantly different (95% CI, -8.0%, 19.7%) (**Table 3**).[2]

Table 3. Cure rates for Staph. aureus infections

	Study	Ceftobiprole group	Control group (Vancomycin)	95% CI
MRSA	Noel, Strauss et al. (2008)	56/61 (91.8%)	54/60 (90.0%)	-8.4, 12.1
	Noel, Bush et al. (2008)	78/87 (89.7%)	31/36 (86.1%)	-8.0, 19.7
MSSA	Noel, Strauss et al. (2008)	121/126 (96.0%)	108/112 (96.4%)	-5.2, 4.4
	Noel, Bush et al. (2008)	150/160 (93.8%)	84/90 (93.3%)	-5.8, 8.2

MRSA = Methicillin-resistant *Staphylococcus aureus*
MSSA = Methicillin-sensitive *Staphylococcus aureus*

Adverse events were also studied in the three randomized control trials. Noel, Strauss et al. reported 52% rate of adverse events in the ceftobiprole group and 51% rate of adverse events in the Vancomycin group.[1] The relative risk increase (RRI) was 0.02 and the absolute risk increase (ARI) was

0.01.[1] The number needed to harm in this study was 100 participants (**Table 4**).[1]

The Noel, Bush et al. study reported an adverse event rate of 56% in the ceftobiprole group and a 57% rate of adverse event rate for the vancomycin plus ceftazidime group.[2] The relative risk increase (RRI) was -0.02 and the absolute risk increase (ARI) was -0.01.[2] The number needed to harm (NNH) in this group was also 100 participants (**Table 4**).[2]

The final study, Schmitt-Hoffmann et al., reported a rate of 83% adverse events in the ceftobiprole group and 50% adverse event rate in the placebo group. The reported relative risk increase (RRI) was 0.66 and the absolute risk increase was 0.33.[3] The number needed to harm in this study was 3 participants (**Table 4**).[3]

Table 4. Incidences of at least one adverse event in Ceftobiprole and Control groups

	Ceftobiprole	Control group	RRI*	ARI*	NNH*
Noel, Strauss et al. (2008)	203/389 (52%)	193/382 (51%)	2%	1%	100
Noel, Bush et al. (2008)	304/543 (56%)	159/279 (57%)	-2%	-1%	-100
Schmitt-Hoffmann et al.	5/6 (83%)	2/4** (50%)	66%	33%	3

*RRI = Relative Risk Increase, ARI = Absolute Risk Increase, NNH = Number Needed to Harm
**Schmitt-Hotffmann compared Ceftobiprole to placebo

The incidence of serious events were also recorded in all three analyzed studies. Serious adverse events were defined as any experience that was life threatening, required hospitalization, or resulted in death.[1,2] In Noel, Strauss et al. 6% of participants in the ceftobiprole group and 6% of participants in the vancomycin group also reported serious adverse events.[1] In Noel, Bush et al. 7% experienced serious adverse events while taking ceftobiprole and 9% while taking vancomycin.[2] The Schmitt-

Hoffmann et al. study reported no serious adverse events (**Table 5)**.[3]

Table 5. Incidence of serious adverse events (AE)

	Ceftobiprole	Vancomycin
Noel, Strauss et al. (2008)	24/398 (6%)	23/382 (6%)
Noel, Bush et al. (2008)	39/543 (7%)	24/279 (9%)
Schmitt-Hoffmann et al.	0/16 (0%)	N/A

Losses to follow up were recorded and all individuals leaving the study were accounted for. In Noel, Strauss et al. 15% of the participants were lost to follow up.[1] The most common reasons for loss to follow up included adverse events or concomitant illness (35 patients), non-cooperation (28 patients), and administrative issues (21 patients).[1] In Noel, Bush et al. 8% discontinued, with most common reason cited as loss to follow up accounting for 3%.[2] There were no patients lost to follow up in Schmitt-Hoffmann et al.[3]

DISCUSSION

One limitation of the Schmitt-Hoffmann et al. safety trial was the duration of treatment. Ceftobiprole was administered for 8 days in this study and adverse effects only measured during that time. The Noel et al. studies used ceftobiprole for an average of 9.0 days and a range of 7-14 days.[1,2] More adverse events may have occurred if the drug was administered for a longer duration. In order to adequately assess safety of a drug it should be tested at the maximum amount of time potentially used by clinicians. This way delayed adverse events can be more accurately measured and thus safety of the drug can be determined.

Another limitation is the clinical cure of infection. This is, by nature, subjective and could have

wide variation based on clinician assessment. The standard used for clinical cure was defined as "resolution of all signs and symptoms of infection," which may have a wide range of meaning and provider to provider dissonance. There is no way to fully eliminate provider subjectivity and this is a perceived weakness in the study.

Another limitation of this review is the fact that both of the main studies determining efficacy were performed by the same lab and headed by the same researcher, Gary Noel. There could be built in bias in reporting results based on researchers desire to produce positive efficacy results. In addition, both of the main studies were funded by Johnson & Johnson Pharmaceuticals who have an invested interest in finding an alternative to vancomycin which is currently mainly produced by a Hospira, a competing Pharmacutical company. More studies need to be performed by other non-biased researchers in order to determine true effectiveness.

At the time this article was written, ceftobiprole was available in Canada and Switzerland but was under review by regulatory authorities and still unavailable in the United States. More research is needed in order for ceftobiprole to be considered a safe and effective alternative to vancomycin and for it to be marketable as such.

One disadvantage to using this medication is that it can only be given intravenously. This limits its use to inpatient care only. In order for a patient to be discharged with a skin infection they need to be managed with a medication by mouth which in this case would require a medication change. Further research would need to be conducted to measure effectiveness of switching from ceftobiprole to a po medication to be taken upon discharge

CONCLUSION

The evidence from these three clinical trials support the conclusion that ceftobiprole is as safe

and effective as vancomycin, the standard treatment for curing complicated skin and skin structure infections. The studies reviewed provide supporting evidence that intervention with ceftobiprole leads to complete resolution of complicated skin and skin structure infections, both microbiologically and clinically. The conclude that ceftobiprole may be considered a reasonable alternative to vancomycin or combination treatments in the event the patient is allergic to vancomycin or the bacteria is vancomycin resistant.

Ceftobiprole is proven effective against gram-positive pathogens, including Staphylococci which is a leading cause of complicated skin and soft tissue infections. It has also been proven effective against MRSA, which is a significant concern for health care providers treating complicated skin infections.

The evidence also shows that ceftobiprole is a safe agent for consumption by patients. Although multiple adverse effects were noted, minimal serious adverse effects were attributed to ceftobiprole in the studies performed. The incidence of adverse effects was on par with or less than the rate of adverse events for vancomycin.

Despite the limitations noted here, the reviewed studies present evidence that ceftobiprole is an effective alternative to vancomycin in treating gram positive complicated skin and skin-structure infections.

REFERENCES

1. Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. *Antimicrobial Agents and Chemotherapy.* Jan, 2008; 52(1):37-44.

2. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clinical Infectious Diseases. 2008;46(5):647-55.

3. Schmitt-Hoffmann A, Nyman L, Roos B, et al. Multiple-dose pharmacokinetics and safety of a novel broad-spectrum cephalosporin (BAL5788) in healthy volunteers. Antimicrobial Agents and Chemotherapy. July, 2004;48(7):2576-80.

4. Klein E, Smith D,Laxminarayan R. Hospitalizations and Deaths Caused by Methicillin-Resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerging Infectious Diseases.* 2007 December; 13(12): 1840–1846.

5. Graham P, Lin S, Larson E (2006). "A U.S. population-based survey of *Staphylococcus aureus* colonization". *Ann Intern Med.* 2006; 144 (5): 318–25.