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ABSTRACT & COMMENTARY

Severe Alcoholic Hepatitis: Prednisolone or Pentoxifylline?

By Kenneth P. Steinberg, MD, FACP, Editor

Professor of Medicine, University of Washington School of Medicine, Seattle, WA

Dr. Steinberg reports no financial relationships in this field of study.

Source: Thursz MR, et al., for the STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015;372:1619–28.

The purpose of this important clinical trial, comparing steroids to pentoxifylline, was done to determine whether either medication would reduce short- and medium-term mortality in patients admitted to the hospital for severe alcoholic hepatitis. The study was a multicenter, randomized, double-blind trial with a 2 x 2 factorial design. Patients were eligible for the study if they had a clinical diagnosis of alcoholic hepatitis. Liver biopsy was not done to confirm the diagnosis. The clinical diagnosis was based on a history of excess alcohol consumption and the absence of other causes of liver disease. They had to have a bilirubin greater than 4.7 mg/dL and a discriminant function of 32 or higher. Key exclusion criteria were jaundice for more than three months, cessation of alcohol consumption for more than two months prior to randomization, the presence of other causes of liver disease, a serum aspartate transaminase level greater than 500 IU per liter or serum alanine transaminase level greater than 300 IU per liter. Patients with renal failure (defined as creatinine > 5.7 mg/dL) active GI bleeding, sepsis, or the need for vasopressor support were also excluded unless the condition stabilized within the first seven days of admission. Enrolled patients were randomly assigned to one of the four study groups: placebo-placebo, prednisolone 40 mg daily plus placebo, placebo plus pentoxifylline 400 mg TID,

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and prednisolone 40 mg daily plus pentoxifylline 400 mg TID. All patients were prescribed treatment for 28 days. The primary outcome was mortality at 28 days. Secondary outcomes included mortality or liver transplantation at 90 days and at one year.

Over a three-year period, 1103 patients were enrolled into the study. The four groups were well matched with regard to baseline characteristics and laboratory abnormalities. The overall mortality at 28 days was 16%, at 90 days was 29%, and at one year 56% of the patients had either died or undergone liver transplantation. There was no interaction between the prednisolone and the pentoxifylline treatments, thus the treatments could be analyzed separately. The mortality for patients treated with prednisolone was 14% compared to 18% in the patients not treated with prednisolone, a difference that did not quite meet standard definitions of statistical significance (OR 0.72, 95% CI 0.52-1.01, p = 0.06). The mortality was not different for patients treated with pentoxifylline (16%) compared to patients not treated with pentoxifylline (16%), (OR 1.07, 0.77-1.49, p = 0.69). In a secondary analysis, multivariate logistic regression adjusting for prognostic variables in alcoholic hepatitis found that the odds ratio for 28-day mortality for patients treated with prednisolone was 0.61 (95% CI, 0.41-0.91; p=0.02) but there was no difference at 90 days or one year.

Serious adverse events were equally distributed across groups except for serious infection that occurred in 13% of those who received prednisolone compared to 7% for those who did not (p=0.002). While infection was more prevalent in the prednisolone groups, infection as a cause of death did not differ across all groups. GI bleeding was not more common in the prednisolone groups.

■ COMMENTARY

This study is an important reminder of the need for rigorous data in the management of common but life-threatening conditions. Alcoholic hepatitis is a highly morbid condition with a high mortality rate. The controversy over the best treatments has persisted for many years, especially over the use of glucocorticoids even despite the presence of meta-analyses on the subject. Some trials have been positive, usually in patients with a discriminant function of 32 or greater, while others have been negative. Systematic reviews have similarly reached different conclusions. The same is true of trials of pentoxifylline where contradictory results have been observed. In this bold study, investigators in the United Kingdom randomized over 1100 patients to prednisolone alone, pentoxifylline alone, placebo alone, or to the combination of prednisolone and pentoxifylline. I believe that this study clearly demonstrates a complete lack of benefit of pentoxifylline in patients with alcoholic hepatitis at all-time points (28 days, 90 days, and one year). The prednisolone results seem less clear. The authors appropriately state that prednisolone did not statistically significantly influence mortality at 28 days, 90 days, or at one year. However, the odds ratio for the effect at 28 days was 0.72, with 95% confidence intervals that barely crossed 1.0 (0.52-1.01) with a P-value of 0.06. Strictly speaking, this is not a statistical difference. But it is extremely close. And in a secondary analysis, a multivariate logistic regression accounting for prognostic variables showed a reduction in mortality with prednisolone at 28 days. However, all survival differences disappeared at 90 days and at one year even in this logistic regression model.

In patients with severe alcoholic hepatitis and a discriminant function of 32 or greater, neither pentoxifylline nor prednisolone impacted medium or long-term outcomes in the best study to date of these treatments. Thus, pentoxifylline appears to have no role in this patient population. It is possible that prednisolone had a trend toward improvement in 28-day mortality especially in the illest patients, but it also clearly led to more serious infections. With the loss of effect at 90 days and one year, it is hard to recommend prednisolone for severe alcoholic hepatitis. Whether this study ends the controversy around glucocorticoids will have to be seen. ■

Endovascular Intracranial Clot Extraction Benefits Are Confirmed in More Clinical Trials

By Matthew E. Fink, MD

SOURCES: Saver J, et al, for the SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; April 17 [Epub ahead of print] DOI:10.1056/NEJMoa1415061.

Jovin TD, et al for the REVASCAT Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; April 17 [Epub ahead of print] DOI: 10.1056/NEJMoa1503780.

Furlan AJ. Editorial. Endovascular therapy for stroke – It's about time. *N Engl J Med* 2015; April 17 [Epub ahead of print] DOI: 10.1056/NEJMe1503217

On April 17, 2015, the *New England Journal of Medicine* published the results of two randomized clinical trials of endovascular stent-retriever clot extraction for ischemic stroke, simultaneous with their presentation at the European Stroke Conference. These two studies, added to those presented and published at the International Stroke Conference in February, bring the total number of studies to five that have shown dramatic benefits of this therapy in appropriately selected patients with acute ischemic stroke.

SWIFT PRIME enrolled 196 patients at 39 centers who were randomized into a thrombectomy group with the stent-retriever plus intravenous TPA compared to intravenous TPA alone within 6 hours of symptom onset. The primary outcome measure was the global disability score as measured by the modified Rankin scale score. The rate of functional independence, a modified Rankin scale score of 0 to 2, was higher in the intervention group than in the control group (60% vs 35%, $P < 0.001$). There were no significant differences between the groups in 90-day mortality or in the rate of symptomatic intracranial hemorrhage (0% vs 3%, $P = 0.12$). This study was terminated early because of the dramatic benefits seen in the early enrollment.

REVASCAT enrolled 206 patients at four centers in Spain, who were randomized to stent-retriever clot extraction vs medical therapy, which could include alteplase, within 8 hours of symptom onset. Once again, using the modified Rankin score as a measurement of global disability at 90 days, there was a dramatic difference in the groups, with the interventional group attaining independence, a modified Rankin score of 0 to 2, in 43.7% vs 28.2% in the medical group. Again, there was no significant difference in the rate of symptomatic intracranial hemorrhage or in mortality between the two groups.

FOLLOWUP

In an accompanying editorial by a pioneer in this field, Dr. Anthony Furlan, the reason for success in these trials was identified as: 1) careful patient selection with documentation of large vessel occlusion, 2) improvement in technology, particularly with the stent retriever device, and 3) rapid speed to enroll and treat patients as quickly as possible.

IS IT WORTH IT?

Endovascular stent retriever therapy for acute ischemic stroke should be considered part of the standard therapy available to neurologists for patients who arrive at their hospitals with acute ischemic stroke, and stroke teams need to focus on speed and efficiency to successfully accomplish these tasks. ■

Ceftolozane/Tazobactam — Formulary Considerations

By Abraham Chang, PharmD

Dr. Chang is a PharmD resident at Stanford University.

Dr. Chang reports no financial relationships relevant to this field of study.

GENERIC NAME: Ceftolozane/tazobactam
TRADE NAME: ZerbaxaTM
FDA APPROVAL DATE: December 19, 2014
U.S. FDA-APPROVED INDICATIONS

• Treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:
• Complicated Intra-abdominal Infections: *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius*
• Complicated Urinary Tract Infections, including pyelonephritis: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Pseudomonas aeruginosa*

PHARMACOLOGY

Ceftolozane is a cephalosporin with a chemical structure similar to ceftazidime. The modified side-chain confers steric hindrance between ceftolozane and entry gate to the 3-position side-chain binding pocket at -lactamase active site, preventing hydrolysis and granting stability against AmpC -lactamase-overproducing *P. aeruginosa*.

Ceftolozane has potent activity against *P. aeruginosa* due to its ability to evade many resistance mechanisms, including efflux pumps, reduced uptake through porins, and modifications of PBP. Ceftolozane has activity against Gram-negative bacteria with classical -lactamases (TEM-1, SHV-1), but is compromised by ESBL and carbapenemases.

The addition of tazobactam extends activity to include most ESBL producers as well as some anaerobic species. However, ceftolozane/tazobactam is not active against bacteria that produce serine carbapenemases (KPC) and metallo-beta lactamases.

PHARMACOKINETICS

Plasma levels do not increase appreciably following multiple IV infusions of up to ceftolozane/tazobactam 2 g/1 g q8h for up to 10 days in healthy adults with normal renal function. The elimination half-life is independent of dose. The human plasma protein binding of ceftolozane and tazobactam is approximately 16-21% and 30%, respectively. The mean steady-state volume of distribution of ceftolozane and tazobactam was 13.5 L and 18.2 L, respectively, similar to extracellular fluid volume. Ceftolozane is eliminated in urine as unchanged parent drug and is not metabolized to any appreciable extent. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1.

ADVERSE EFFECTS

The most common adverse reactions (greater than 5% of patients) in patients were nausea, diarrhea, headache, and pyrexia. In the cIAI trials (phase 2 and 3), death occurred in 2.5% of patients receiving ceftolozane/tazobactam and in 1.5% of patients receiving meropenem. The causes of death varied and included worsening and/or complications of infection, surgery, and underlying conditions.

CONTRAINDICATIONS/ WARNINGS/PRECAUTIONS

• Contraindicated in patients with known hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the beta-lactam class.

Pharmacokinetics

PK parameters	Ceftolozane/Tazobactam (1 g/0.5 g q8h)			
	Ceftolozane		Tazobactam	
	Day 1 (n = 9)	Day 10 (n = 10)	Day 1 (n = 9)	Day 10 (n = 10)
C_{max} (mcg/mL)	69.1	74.4	18.4	18
t_{max} (h)	1.02	1.07	1.02	1.01
AUC (mcg*h/mL)	172	182	24.4	25
$t_{½}$ (h)	2.77	3.12	0.91	1.03

CLINICAL TRIALS/EVIDENCE SUMMARY

Trial	Patient Population	Intervention	Efficacy Results	Adverse Effects
ASPECT-cUTI Phase 3, multi-center, prospective, double-blind, randomized study	N =1068 hospitalized, adult patients with cUTI, including pyelonephritis	Ceftolozane/ tazobactam 1.5 g IV q8 vs Levofloxacin 750 mg IV q24h x 7 days	TREATMENT ARMS / MMITT N / MMITT CURE / ME N / ME CURE Ceftolozane/ tazobactam: 398 / 76.9% / 341 / 83.3% Levofloxacin: 402 / 68.4% / 353 / 75.4% Ceftolozane/tazobactam met primary and secondary endpoints achieving non-inferiority to levofloxacin with regard to composite clinical and microbiological cure.	The most commonly reported adverse events were headache (5.8%), constipation (3.9%), hypertension (3%), nausea (2.8%), and diarrhea (1.9%)
ASPECT-cIAI Phase 3, multi-center, prospective, double-blind, randomized study	N = 993 hospitalized, adult patients with cIAI	Ceftolozane/ tazobactam 1.5 g IV q8 + Metronidazole 500 mg IV q8h vs Meropenem 1 g IV q8h x 4-14 days	TREATMENT ARMS / MMITT N / MMITT CURE / ME N / ME CURE Ceftolozane/ tazobactam + metronidazole: 389 / 83% / 275 / 94.2% Meropenem: 417 / 87.3% / 321 / 94.7% Ceftolozane/tazobactam met primary and secondary endpoints achieving non-inferiority to meropenem with regard to clinical cure.	The most commonly reported adverse events were nausea (7.9%), diarrhea (6.2%), pyrexia (5.2%), insomnia (3.5%), and vomiting (3.3%).

cUTI = complicated urinary tract infection; cIAI = complicated intra-abdominal infection; mMITT = microbiological modified intent-to-treat; MITT = microbiological intent-to-treat; ME = microbiologically evaluable

• Decreased efficacy in patients with baseline CrCl of 30 - ≤ 50 mL/min: Subgroup analysis of a phase 3 cIAI trial found clinical cure rates were lower in patients with baseline CrCl of 30 - ≤ 50 mL/min compared to those with CrCl ≥ 50 mL/min. A similar trend was also seen in the cUTI trial.

• Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.

• *Clostridium difficile*-associated diarrhea: *Clostridium difficile*-associated diarrhea has been reported for nearly all systemic antibacterial agents, including ceftolozane/tazobactam.

• Development of Drug-Resistant Bacteria: Prescribing ceftolozane/tazobactam in the absence of a proven or strongly suspected bacterial infection is unlikely to benefit the patient and risks the development of drug-resistant bacteria.

Pregnancy and Lactation Information

• Pregnancy category B: Embryo-fetal development studies performed with IV ceftolozane in mice and rats revealed no evidence of harm to fetus.

• It is not known whether ceftolozane or tazobactam is excreted in human milk.

DRUG INTERACTIONS

No significant drug-drug interactions are anticipated between ceftolozane/tazobactam and substrates, inhibitors, and inducers of cytochrome P450 enzymes.

DOSAGE AND ADMINISTRATION[1]

Recommended dose

• cIAI: 1.5 g IV every 8 hours infused over 1 hour for 4-14 days.

• cUTI: 1.5 g IV every 8 hours infused over 1 hour for 7 days.

• Patients with renal impairment

• CrCl: 30-50 mL/min: 750 mg IV every 8 hours.

• CrCl: 15-20 mL/min: 375 mg IV every 8 hours.

• ESRD on HD: A single loading dose of 750 mg IV followed by 150 mg IV every 8 hours. On hemodialysis days, administer dose at the earliest time following completion of dialysis.

CONCLUSIONS

Ceftolozane/tazobactam is a cephalosporin and βlactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli, including ESBL-producing *Enterobacteriaceae* and drug-resistant

Cost

	How Supplied	Average Wholesale Price (each vial)	Usual Dose	Cost of Therapy per day
Ceftolozane/ tazobactam	1.5 g vials	$99.60	1.5 g q8h	$298.80
Meropenem	1 g vials	$18.48	1 g q8h	$55.44

P. aeruginosa. It possesses a safety and tolerability profile similar to other βlactam antibiotics. However, its lack of activity against KPC and MBL enzymes is a limitation.

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ABSTRACT & COMMENTARY

Blood Transfusion After Cardiac Surgery

By Michael H. Crawford, MD, Editor.

Dr. Crawford reports no financial relationships relevant to this field of study.

SOURCE: Murphy GJ, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;372:997-1008.

Due to the cost of blood transfusions and the lack of data supporting liberal transfusion policies, newer guidelines recommend more restrictive transfusion thresholds (e.g., hemoglobin < 7 g/dL). However, many believe cardiac surgery is an exception due to the myocardium's high oxygen requirement. Thus, these investigators performed the Transfusion Indication Threshold Reduction (TITRe2) trial to determine if a restrictive transfusion threshold would reduce postoperative morbidity and health care cost. In 17 United Kingdom (UK) cardiac surgery centers, 2003 patients were randomized to a restrictive threshold of < 7.5g/dL or a liberal threshold of < 9g/dL, with transfusions administered to help the hemoglobin above these thresholds. The patients were followed for 3 months for the primary outcome of serious infections or an ischemic event in the brain, heart, gut, or kidney. Median age of the patients was 70 years old, and 69% were men. Most had coronary bypass (41%) or valve surgery (31%). One-quarter of the patients received a transfusion before being enrolled. A median of one unit of red cells was transfused in the restrictive group and two in the liberal group. Transfusions were given to 64% of the restrictive group and 95% of the liberal group.

The primary outcome was seen in 35% of the restrictive group and 33% of the liberal group (P = NS). The rates of pulmonary complications and the length of ICU stay did not differ between groups. There were more deaths in the restrictive group (4.2% vs 2.6%; HR, 1.64; 95% CI, 1.0-2.7, P = 0.045). Overall costs were no different between the two groups. The authors concluded that a restrictive transfusion policy after cardiac surgery was not superior to a more liberal policy, and overall costs were similar.

■ COMMENTARY

Currently, transfusion rates in the UK and the United States are highly variable between cardiac surgery centers (8-93%). Part of this wide variation in practice is the controversy in the literature. Observational studies that showed higher risks of mortality and morbidity with liberal transfusion policy were confounded by patient characteristics that influenced transfusion decisions. The few comparative trials done lacked statistical power. This study largely avoided these pitfalls and failed to prove the hypothesis that bad outcomes and costs would be higher with a liberal transfusion policy. Concerning was the results of the secondary outcome variable of death, which were almost twice as high in the restrictive group. Also, this difference persisted despite sensitivity analyses. In addition, patients who already got a transfusion before being enrolled in the trial were excluded. When rising creatinine was added to the primary endpoint, the results favored a liberal policy.

The more liberal approach is clinically plausible when you consider that ischemic myocardium needs oxygen delivery, which makes the cardiac surgery setting different from other settings with blood loss. Thus, I believe allowing clinicians to use their own judgment with cardiac surgery patients, rather than being constrained by hospital policy, makes the most sense for now. ■

ABSTRACT & COMMENTARY

Pneumonia in U.S. Children Requiring Hospitalization

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Chairman, Department of Medicine, Santa Clara Valley Medical Center, Clinical Professor of Medicine and Pediatrics (Affiliated), Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Two thousand six hundred thirty-eight children with a clinical diagnosis of community-acquired pneumonia (CAP) were enrolled in a prospective surveillance study. Eighty-nine percent had radiographic evidence of pneumonia. The median age of children hospitalized was 2 years, with the highest rates seen in children younger than 2 years. Respiratory viruses were the most commonly detected pathogens.

SOURCE: Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015;372:835-845.

Two thousand six hundred thirty-eight of 3803 eligible children were enrolled from January 2010 through June 2012 in a prospective study of children younger than 18 years old requiring hospitalization at three children's hospitals in the United States (Memphis, Nashville, and Salt Lake City). Children with recent hospitalization or severe immunosuppression history were excluded. Blood and respiratory specimens were collected for pathogen detection by traditional cultures and PCR. Chest X-rays were independently reviewed by a panel of study radiologists.

Eighty-nine percent of children hospitalized had radiographic evidence of pneumonia. The mean age was 2 years old. Twenty-one percent of children required admission to intensive care units, 7% required mechanical ventilation, and 3 children (1%) died. Thirty-three percent of children had underlying asthma or reactive airway disease, and 21% of children younger than 2 years old had a history of preterm birth. Among the 2222 children with radiographic evidence of pneumonia, a viral or bacterial pathogen was detected in 81%, one or more viruses in 66%, bacteria in 8%, and both bacterial and viral pathogens in 7%. The overall incidence of CAP requiring hospitalization in children was 15.7 cases/10,000 children and the highest rate was in children younger than 2 years, in whom the rate was 62.2 cases/10,000 children.

Respiratory syncytial virus (RSV) was more common in children younger than 5 years of age than in older children (37% vs. 8%), as were adenovirus (15% vs. 3%), and human metapneumovirus (HMPV) (15% vs. 8%). Together, HMPV, adenovirus, parainfluenza virus, and coronavirus accounted for one-third of pathogens detected, with the highest rates seen in children younger than 5 years old. As expected, RSV peaked sharply in the winter months. Human rhinovirus was detected in 27% of children with pneumonia. Bacterial pathogens were detected in 15% of children with pneumonia. *Streptococcus pneumoniae* was detected in just 79 cases (2%) and was roughly equal in younger and older children. *Mycoplasma pneumoniae* was more common in children older than 5 years of age than in younger children (19% vs. 3%).

■ COMMENTARY

This paper presents a nice update on the etiology of CAP in children requiring hospitalization and used modern sensitive laboratory methods to reveal an etiology of infection in a high percentage of patients studied. The study reinforces the importance of CAP requiring hospitalization being of much higher incidence in very young children. Of note in this study was the predominance of viral vs. bacterial pathogens identified in this study (71% vs. 15%), with some overlap in cases in which both viral and bacterial pathogens were identified. The predominance of viral pathogens, especially in young children, was striking and likely reflects both the direct effects (and herd immunity effects) of the use of both pneumococcal conjugate vaccine and HiB vaccine. It should also be noted that this study took place after the 2009-2010 pandemic of Influenza A (H1N1), which would have made the incidence of influenza virus more common than was seen in this study. ■

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CME QUESTIONS

1. What results were found in the multicenter; randomized control trial of prednisolone or pentoxifylline for severe alcohol hepatitis (STOPAH trial)?

a. An increase in severe infections in patients treated with prednisolone
b. No statistically significant difference in mortality with pentoxifylline
c. No statistically significant difference in mortality with prednisone
d. No difference in gastrointestinal bleeding in patients treated with prednisolone compared to placebo
e. All of the above

2. In the study by Murphy and colleagues of a liberal versus a restrictive transfusion threshold after cardiac surgery, a restrictive transfusion policy was:

a. Superior to a liberal policy with regards to all outcomes and was associated with lower costs
b. Not superior to a liberal policy with regards to all outcomes and with equivalent costs
c. Inferior to a liberal policy with higher mortality and higher costs
d. More expensive

3. Which pathogen(s) was the most common etiology of pneumonia in the study by Jain and colleagues in children hospitalized for community-acquired pneumonia:

a. *Streptococcus pneumoniae*
b. *H. influenzae*
c. *Mycoplasma pneumoniae*
d. Viruses

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

[IN FUTURE ISSUES]

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