

# Endotoxin Removal: Bringing the Mission to North America

Debra Foster<sup>a</sup> David J. Klein<sup>b</sup> Gualtiero Guadagni<sup>a</sup> Paul M. Walker<sup>a</sup>

<sup>a</sup>Spectral Diagnostics Inc., <sup>b</sup>Department of Critical Care, and the Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ont., Canada

## Key Words

EUPHRATES trial · Sepsis · Polymyxin B · Blinded trial

## Abstract

The EUPHRATES trial (Evaluating Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock) is the first biomarker-driven trial in sepsis. This unique trial is being run in a blinded manner, further contributing to the robustness of its design. This paper will describe the implementation of the EUPHRATES trial focusing on 3 pertinent features: (1) managing (and maintaining) the blinding of a medical device trial; (2) impact of the use of a diagnostic test where eligible subjects with septic shock must also have high levels of endotoxin ( $\geq 0.60$  EAA units), and (3) managing enrolment in a complicated trial design where two medical teams are involved (the intensivist as the blinded caregiver and nephrologists as the unblinded performers of the intervention). The study is nearing the halfway mark and is currently experiencing excellent recruitment success.

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## Introduction

A large body of evidence exists in the medical literature that demonstrates a high degree of safety for the clinical use of a polymyxin B direct hemoperfusion cartridge

(PMX) as well as its efficacy in removing endotoxin and reducing mortality in patients with severe sepsis and septic shock.

Systemic use of polymyxin B is associated with a 'black box' warning from the US Food and Drug Administration (FDA) due to risks of nephrotoxicity and neurotoxicity. However, in the two largest randomized controlled trials conducted outside of Japan, by Vincent et al. [1] and Cruz et al. [2], no evidence of nephrotoxicity or neurotoxicity was noted with PMX cartridge use. In addition, there has been no evidence of systemic release of polymyxin B in human and animal studies of Toraymyxin.

In mid-2009, armed with the compendium of published evidence and results from the recently completed EUPHAS trial, Spectral Diagnostics applied for and received approval from the Center for Devices and Radiologic Health of the FDA for an investigational device exemption (IDE) for the EUPHRATES trial (Evaluating Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock).

The EUPHRATES trial is a double-blind, randomized, controlled trial of standard medical care plus the PMX cartridge versus standard medical care alone in subjects with endotoxemia and septic shock. Approximately 50 clinical investigative sites in the USA and Canada will participate in this study, with an expected enrolment of 360 subjects (180 per treatment arm including 15% attrition rate). Subjects in intensive care units (ICUs) will be

assessed for septic shock using known or suspected infection and hypotension requiring vasopressor support as the primary criteria. If a patient meets all entry criteria based on clinical criteria, they (or a surrogate decision maker) will then be approached for consent to a blood draw to determine if there is the presence of an elevated endotoxin level ( $\geq 0.60$  EAA units) using the Endotoxin Activity Assay (EAA<sup>TM</sup>).

If the EAA is high ( $\geq 0.60$  EAA units), the subject or their surrogate will be approached for consent for possible treatment with PMX. To be randomized, the full inclusion/exclusion criteria must continue to be met, as determined in conjunction with a clinical coordination center. Randomized patients receive either standard medical care for septic shock as per the Surviving Sepsis Campaign guidelines [6] or standard medical care plus the PMX cartridge (administered twice for 1.5–2 h per cartridge, approx. 24 h apart). The status of all subjects is followed by clinicians using standard procedures with EAA measurements performed four times during the first 72 h. After 72 h, subjects will have detailed assessments on day 7, and then efficacy and safety clinical assessments at weekly intervals through day 28 while in the hospital. For all subjects, a follow-up visit or telephone call to determine their mortality status will take place after approximately 3 months (i.e. day 90), and at 6 months and 12 months after the subject is randomized.

If the EAA is not high, a second test is permitted by protocol. For otherwise eligible patients with low EAAs data is collected using a minimal dataset including 28-day mortality.

This study has unique features unlike all other trials of the PMX cartridge. Firstly, the FDA strongly recommended that the study design include double blinding; secondly, eligibility requires the results of the EAA and, thirdly, the sample size estimate is 360 subjects, thereby establishing the EUPHRATES trial as the largest randomized study ever using the PMX cartridge.

### **Maintaining the Blinded Element of a Medical Device Trial**

To maintain the trial's blinded element, the ICU physician investigators, those healthcare professionals involved in recording blinded data, and those who are involved in data analysis (except an independent statistician), are blinded to the allocation of treatment. In many North American hospitals, acute dialysis and other forms of renal replacement therapy are under the domain of ne-

phrologists. This allows for a study design that includes two medical teams; nephrologists, who provide unblinded study interventions, and intensivists, who manage patients care blinded to the study treatment allocation. Specifically, a nephrology staff member, the ICU bedside nurse and a pharmacist will know the treatment allocation and record allocation and treatment records (timing of device use) and concomitant anticoagulant medication administered (e.g. heparin) on study data collection sheets that are kept blinded from the remaining study personnel.

Nephrology staff are trained to use the PMX cartridge on those subjects randomized to the PMX cartridge group and to maintain the blind for the subjects that are randomized to standard of care by the performing of a sham perfusion event. Study staff (the principal investigator and other ICU personnel involved in the subjects care) and the subject (and/or the subjects surrogate) all remain blinded to the treatment arm. Study eligibility EAA results are known to the treating physician, but all subsequent EAA results are blinded.

The sham perfusion is performed as follows: there is no actual sham cartridge, instead a tube of the same dimension and approximate weight of the PMX cartridge is packaged in a sealed outer carton that is identical to that used for the PMX cartridge. No central venous dialysis catheter is inserted and no hemoperfusion occurs. Instead, a member of the unblinded medical team performs a sham insertion, mimicking all the steps of an actual line insertion except that a dialysis catheter is cut and affixed to the skin in the area of the typical femoral vein access and an opaque dressing applied as if the catheter was inserted into the vein. The access ports are exposed. During the 2-hour period of sham perfusion, a blood pump and associated tubing is wheeled to the subject's bedside. The machine is on, and if feasible, operates in a recirculation mode wherein the return line is connected to the withdrawal line and the subject is out of the circuit. This is performed at the patient's bedside with the curtains drawn and sites are instructed to minimize the visibility of the tubing so as not to expose the treatment allocation.

### **Use of a Diagnostic Test**

The EUPHRATES trial is the first interventional study in sepsis to require a threshold level of a specific biomarker in order to be randomized to receive potential treatment. Moreover, the measured analyte, endotoxin, is the most well-studied and potent mediator of the disease pro-

cess and the treatment is specifically targeted at its direct removal. This direct link between a diagnostic and therapeutic, or so-called theragnostic, approach is meant to address some of the important criticisms of past negative sepsis trials that have relied on traditional clinical criteria based on variations in SIRS criteria and the ACCP/SCCM consensus sepsis definitions. The EUPHRATES trial is unique in this approach and preliminary data confirms that approximately 50% of otherwise eligible patients have EAA <0.6. This group has a mortality rate of approximately 25%, lower than the composite mortality rate of the randomized group at approximately 33%.

This 'personalized medicine' approach is novel to the ICU but, in fact, is already revolutionizing other areas of medicine including oncology and cardiology. Tyrosine kinase inhibitors for patients with specific mutations in lung cancer, renal cell carcinoma and some hematologic malignancies have dramatically changed mortality from these disease subsets. Patient-specific drug metabolism profiles are now routinely being used to choose personalized anticoagulation regimens in acute coronary syndrome. In the ICU, the International Sepsis Federation has issued a declaration calling 'to transform the diagnosis of sepsis from a physiologic syndrome into one or more biochemical disorders'. From a practical and statistical perspective, this personalized approach should have the benefit of allowing for greater treatment effects in smaller sample sizes of patients most likely to benefit from the therapy. In the EUPHRATES trial, it has been estimated that the current sample size of 360 patients would be equivalent to a similar study with 1,200 patients if no biomarker was used to enrich the study population.

### Managing Enrolment

Recruitment targets/timelines in the original IDE application were based on the plan to initiate 20 US sites. Sites would be expected to enroll 1 subject per month for a total of approximately 18 subjects over 18 months per site. Trials targeting a similar population had a predicted enrolment rate of 5–10 subjects per site. This is well below the EUPHRATES study projected rate of 18 subjects per site for 20 sites. For example, the Eli Lilly-sponsored PROWESS trial [3] enrolled 1,690 subjects in 164 sites (average of 10 subjects per site) and the Eli Lilly-sponsored ADDRESS trial [4] included 516 sites and enrolled 2,640 subjects (5 subjects per site). The Eisai-sponsored trial [5] plans were to enroll 2,000 patients at approximately 159 sites (13 subjects per site).

However, the number of sites participating in the EUPHRATES study was initially limited to 15 by the FDA during their review of the IDE. They were concerned that the inclusion of too many sites may introduce bias which would make it difficult to pool all the data at the end of the study. The reduced number of sites sanctioned by the FDA and the small increase in sample size required an increase in the enrolment rate to 24 subjects per site. To meet the recruitment timeline of 28 months for the EUPHRATES study, 15 sites would have to enroll at least 0.86 subjects per month per site.

Study enrolment got off to a slow start. At the end of 2012 there were only 78 subjects enrolled. An aggressive recruitment plan was implemented for 2013, which consisted of the following elements:

(1) The FDA was successfully approached to allow for up to 60 recruiting sites in the USA and Canada.

(2) Recognition that the stakeholders for meeting recruitment targets are the sponsor, contract research organization and sites as equal partners.

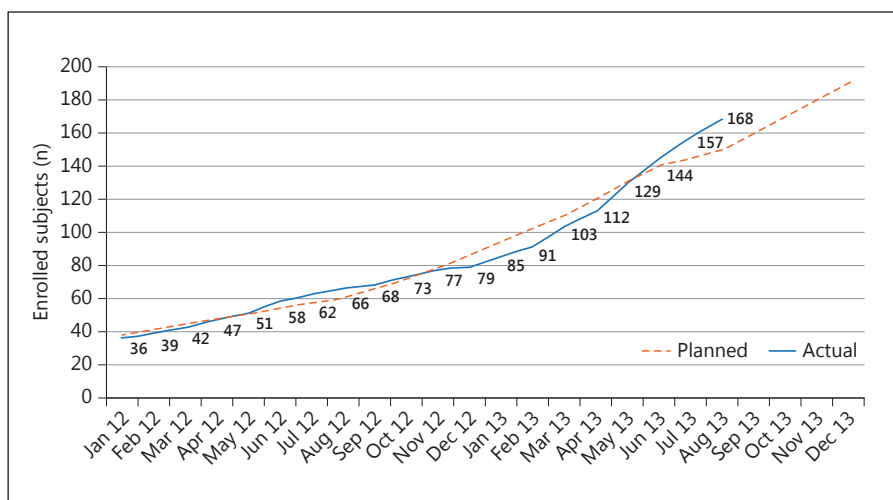
(3) A strict site-selection process was implemented that included as a minimum: (i) ability to meet recruitment targets (number of ICU beds, appropriate patient demographics, enrolment rates from previous sepsis trials); (ii) ability to identify a nephrologist sub-investigator with access to hemoperfusion devices; (iii) capability of 24-hour screening, and (iv) experience with sepsis/ICU clinical trials (established infrastructure for trials).

(4) Creation of a web-based prescreening log to capture potentially eligible subjects and reasons for non-enrolment, including due to EAA <0.60 units.

(5) Hiring of a full-time recruitment specialist and formation of a recruitment committee.

The duties of the recruitment specialist are to visit each study site within 2–3 weeks of study start-up to ensure screening processes are in place and, if necessary, to perform a mock enrolment so as to ready the site for the first subject. In addition, the recruitment specialist visits all study sites on a rotating basis to review screening techniques, provide tools as necessary and to identify gaps and/or share best practices between sites in boosting recruitment rates.

The recruitment committee meets on a monthly basis. Metrics are reviewed including the site-by-site recruitment rate (subjects per site per month) and overall study recruitment rate. Prescreening activities are evaluated and site visit reports from the recruitment specialist are discussed. In addition, the committee is responsible for promoting a positive team spirit amongst EUPHRATES study sites by ensuring monthly recruitment, and study



**Fig. 1.** The EUPHRATES study recruitment curve, predicted versus actual: January 2012 to December 2013.

status updates are communicated (e-mailed) to all study sites, quarterly newsletters are issued and investigator meetings planned. The result of these recruitment strategies is presented in figure 1.

The recruitment rate per study year doubled in 2013 compared to 2011. In 2011, the rate was 0.17 subjects per site per year; in 2012 it was 0.20, and for 2013 the EUPHRATES study is enjoying 0.35 subjects per site per year. At this rate, the planned mid-term interim analysis will occur in early 2014.

## Conclusion

The EUPHRATES trial has incorporated a number of unique features compared to previous sepsis trials. The inclusion of sites has been limited in number and location (North America). In addition to meeting the clinical en-

try criteria, a biomarker is required for randomization. The EUPHRATES trial becomes a new high-water mark for device evaluation with the addition of the blinding method and its impact on increased internal validity of the study results. An individualized recruiting strategy for each site and the use of a recruitment specialist has resulted in an increase in the recruiting rates over time. When used in practice the combination of clinical and biomarker assessments will make it possible to identify patients most likely to benefit from the treatment, a significant step forward in the treatment of septic patients.

## Disclosure Statement

Dr. Walker is CEO of Spectral Diagnostics, Inc., Toronto, Canada (SDI); Dr. Guadagni and Debra Foster are Vice Presidents of SDI. Dr. Klein is a paid consultant for SDI as well as Staff Physician, Department of Critical Care, St. Michaels Hospital.

## References

- 1 Vincent JL, Laterre PF, Cohen J, et al: A pilot-controlled study of a polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. *Shock* 2005;23:400–405.
- 2 Antonelli M, Fumagalli R, Cruz DN, et al: PMX endotoxin removal in the clinical practice: results from the EUPHAS trial. *Contrib Nephrol* 2010;167:83–90.
- 3 Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
- 4 Laterre PF, Abraham E, Janes JM, et al: AD-DRESS trial (ADministration of DRotrecogin alfa [activated] in Early stage Severe Sepsis) long-term follow-up: one-year safety and efficacy evaluation. *Crit Care Med* 2007;35:1457–1463.
- 5 Opal SM, Laterre PF, Francois B, et al: Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA* 2013;309:1154–1162.
- 6 Dellinger RP, Levy MM, Rhodes A, et al: Surviving sepsis campaign: international guidelines for the management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.