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14. ABSTRACT The Crozer Burn Treatment Center has been under contract with the U.S. Army Institute for Surgical Research in conjunction with the Army Burn Center since 2007 to carry out two studies under protocols established by Army researchers. Study 1 is "Automated Fluid Resuscitation of Burn Patients". Study 2 is "Evaluation of Aquacel Ag for Autogenous Skin Donor Sites". Study 1: We completed enrollment of 11 patients after screening 1,285 patients since January 2011. All study-related data has been transmitted to the USAISR for analysis. By entering these patients into the larger data collection project, this project has contributed to the Army's development of the next stages of "Closed-Loop" fluid resuscitation that will automatically titrate fluid therapy to changes in urinary output. We found that the use of the decision support system resulted in staff being more conscious of their fluid resuscitation efforts. Use of the digital urimeter allowed for more accurate urine output measurements. The Ab-Viser was an excellent tool for measuring bladder pressure. This technology will improve outcomes for returning military burn patients by providing guidance to providers on best practices. Study 2: During the entire period, which began in March 2009, a total of 2,136 patients were screened. 34 patients were enrolled and 29 completed the study. Study 2 is now complete. This study was presented as a poster at the 2013 ABA annual meeting. This study contributed to knowledge regarding use of Aquacel Ag as a dressing for autogenous skin donor sites compared to current standard donor site care in the injured burn patient. The study is important to soft tissue trauma and burn research because expediting wound healing helps return injured service members to full military duty. The study found that Xeroform (usual care) was the preferred topical wound dressing when compared to Aquacel Ag, which contradicted the study hypothesis. A manuscript is currently being prepared for submission to the Journal of Burn Care and Research. Study 3: Acinetobacter baumannii was eliminated from the Crozer burn center in 2007, therefore Crozer carried out other research projects, as described in this report.					
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INTRODUCTION:

The purpose of the proposed project was to conduct burn research that would benefit combat casualties in the current conflict. The Army Burn Center, which is part of the Brooke Army Medical Center in Fort Sam Houston, Texas, has demonstrated the applicability of burn research in civilian populations to combat populations. The Nathan Speare Regional Burn Treatment Center was under contract with the U. S. Army Institute for Surgical Research to carry out two projects according to protocols that have been already established by Army researchers. A third project was defined by Crozer's Principal Investigator. These projects were:

Study 1: "Automated Fluid Resuscitation of Burn Patients"

The purpose of Study 1 was to collect data which would be used to create an effective resuscitation algorithm for the development of a closed loop resuscitation system. The actual use of the closed loop resuscitation system will occur in a future study. Approximately 20 patients needed to be enrolled. The project was expected to improve resuscitation of burn patients by creating a feedback loop of actual patient response to resuscitation volumes, and titration of fluid therapy to changes in urinary output. Data from urimeters, cardiac monitors, and IV pumps were measured at 10-minute intervals and fed to a DAQ, which is a computer system designed to collect data from this equipment at the bedside.

Study 2: "Evaluation of Aquacel Ag Dressing for Autogenous Skin Donor Sites"

This study compared the performance of an agreed upon dressing to the normal standard of care (Xeroform). Patients who were scheduled for excision and split thickness skin grafting of burns had one of two donor sites covered with the Aquacel Ag dressing, and the other treated according to standard care. Approximately 30 patients were to be enrolled. The hypothesis was that mean healing time for wounds treated with Aquacel Ag dressing would be less than the mean healing time for wounds treated with Xeroform dressing. Specific aims were: 1) that pain as perceived by the patient would be equal to or less than with the Aquacel Ag dressing as compared with the standard dressing, and 2) the cosmetic effect of healing at post surgery day 30-45 would be equal or less with the Aquacel Ag dressing as compared with the standard of care dressing.

Study 3: A Comparison of Clinical and Microbiological Efficacy of Three Separate Antibiotic Regimens against *Acinetobacter baumannii*.

A. baumannii has been steadily emerging as a poly-resistant organism in burn treatment centers. In addition to the problem of widespread colonization of patient care areas, there has been the progressive development of multiple resistance genes. The goal of this project was to evaluate the microbiological and clinical efficacy of three potential antimicrobial agents over 24-months in three groups of 20 adult patients with documented *A. baumannii* infections to determine if there are any subtle or frank differences in outcome with the use of these antimicrobials. Using standard manufacturer-recommended doses, we intended to compare two agents that have not been routinely used, colistin and tigacycline, to imipenem-cilistatin to guide best practices in *A. baumannii* treatment. Using standard statistical testing methods the duration of treatment, time to onset of infection, and other parameters would have been investigated. Standard assessment of infection response would have been used to evaluate and compare these three agents. Pilot data on Crozer burn patients with *A. baumannii* pneumonia was also to be analyzed. This study did not materialize because Crozer did not have any patients that met the criteria for inclusion during the study period. In order to fully utilize the burn research nurse, we have worked on other projects applicable to the military theatre which have contributed to other areas of burn research.

BODY:

The approved Statement of Work is as follows:

Study 1, Protocol Title: “Automated Fluid Resuscitation of Burn Patients – Phase 1”

Task 1: To collect data from 20 study subjects which will be used to create an effective resuscitation algorithm for the development of a closed loop resuscitation system.

- a. Complete project start-up activities (hiring and training of research staff, purchasing equipment) (Year 1, Quarter 1)
- b. Enroll 15 study subjects and collect data (Year 1, Quarters 2-4)
- c. Enroll 5 study subjects and collect data (Year 2, Quarter 1)

Study 2, Protocol Title: “Evaluation of Aquacel Ag for Autogenous Skin Donor Sites”

Task 1: Enroll up to 30 patients in this multi-center trial to evaluate the performance of the identified dressing versus standard of care dressing (Xeroform) for skin donor sites in terms of day of healing, comfort, cosmetics and ease of use.

- a. Complete project start-up activities (hiring and training of research staff) (Year 1, Quarter 1)
- b. Enroll 75% of study subjects, harvest subject’s donor sites, randomize dressing to donor sites, and conduct clinical assessments (Year 1, Quarter 2-4)
- c. Enroll 25% of study subjects, harvest subject’s donor sites, randomize dressing to donor sites, and conduct clinical assessments (Year 2, Quarter 1)
- d. Summarize results (Year 2, Quarter 1)

Study 3, Protocol Title: “A Comparison of Clinical and Microbiological Efficacy of Three Antibiotic Regimens against *Acinetobacter baumannii*”

Task 1: To collect data from three groups of 40 patients and to compare the responses to antibiotic therapy with specific focus on: 1) differences in duration of therapy; 2) differences in time to eradication of infection (laboratory findings changes, vital signs, culture results); 3) differences in adverse reaction profiles of the patients; and 4) impact on the susceptibility of *A. baumannii* to these agents over a two year period.

- a. Complete project start-up activities (hiring and training research staff) (year 1, quarter 1)
- b. Enroll 45 subjects and collect data (year 1, quarters 2-4)
- c. Enroll 15 subjects and collect data (year 2, quarters 1)
- d. Enroll 60 additional subjects (year 2, quarters 2-4, Year 3, quarter 1)
- e. Compose report, submit abstract for national meeting presentation, write manuscript for publication (year 4, quarter 2)

(Note: ‘d’ and ‘e’ will extend beyond the grant period. See Proposal Narrative)

KEY RESEARCH ACCOMPLISHMENTS:

Study 1 (Resuscitation Study)

- This study was conducted to assist the military in testing the decision support system as the first step in developing a full “closed-loop” resuscitation system that will automatically titrate fluid therapy to changes in urinary output. This would benefit medical personnel in mass casualty scenarios in civilian and military populations and those treating individual patients with large burns in burn centers. Through this study, we found that the use of the decision support system resulted in staff being more conscious of their fluid resuscitation efforts. Use of the digital urimeter allowed for more accurate urine output measurements. The Ab-Viser was an excellent tool for measuring bladder pressure and we are in the process of bringing the product into our health system. Though we were only able to collect a limited amount of data, we hope that this information further assists the military in developing a “closed-loop” resuscitation system.
- We completed 55% of our enrollment target for Study 1 by enrolling 11 of the 20 required patients. Varying amounts of data were collected on 10 patients, with 3 completing the full 48 hours on the study. All study-related data has been sent to the USAISR for analysis.

Study 2 (Donor Site Study)

- This study was conducted to assist the military in finding easy to use topical wound dressings in the battlefield that will expedite wound healing. Through our research we determined that Xeroform is much easier to use than Aquacel Ag and potentially more cost effective, though cost was not evaluated as part of the study. Donor sites treated with Xeroform healed faster and had a more favorable cosmetic outcome than those treated with Aquacel Ag. Overall, the patients preferred Xeroform.
- Enrollment is complete. A total of 2,136 patients were screened during the entire study period with 34 patients enrolled and 29 completing the study. This study was presented as a poster at the 2013 American Burn Association Annual Meeting. Currently, the manuscript is being written, which we plan to submit to the Journal of Burn Care and Research for publication.

Study 3 (Poly-resistant acinetobacter baumannii)

- Study 3, a project defined by Crozer, was not begun because Crozer did not have any patients that met the criteria for inclusion since April, 2008. The study was focused on the poly-resistant *A. Baumannii*, which was eliminated in the burn unit in 2007 and has not recurred. In order to fully utilize the burn research nurse, we have worked on other projects applicable to the military theatre which have contributed to other areas of burn research. During the full study period, we have been involved in the following activities:

FY 2012-2013

Study 1 (Resuscitation Study)

We continued to screen every admission on a 24/7 basis with on-call coverage of the research team. During FY 2012-2013, a total of 502 patients were screened. 19 patients had a TBSA \geq 20%. 4 patients were enrolled. 0 patients completed the full 48 hours on the study. 1 patient was made a DNR and was removed from system before expiration. 1 patient required surgery in the OR during the resuscitative phase and 2 computer malfunctions occurred. The other 15 patients with \geq 20% TBSA were excluded for a variety of reasons: 5-unable to obtain consent, 3-age, 7-did not require CVC and/or foley.

The computer continued to freeze and cease data collection around the 20-24 hour mark. We have communicated with the Army engineer and Jose Salinas regarding the issue on many occasions. Delay in software validation was noted as the issue. Data transfer to the Army remains an issue due to the large file size. We are still working with our IS department to resolve this issue.

The strict inclusion criteria continued to be an issue with enrollment. The Crozer IRB required consent IN PERSON. After discussing the issue with the IRB several times, they agreed to allow us to obtain phone consent, but enrollment continues to be an issue. Family members did not return phone calls or there was no family available to give consent.

Study 2 (Donor Site Study)

Enrollment is complete. A total of 502 patients were screened during FY 2012-2013. 3 patients were enrolled and 3 completed the study.

For the entire study period, a total of 34 were enrolled with 29 patients completing the study. This study was presented as a poster at the 2013 American Burn Association Annual Meeting.

IRB-Approved Projects FY 2012-2013

- Retrospective review of the experience of the Nathan Speare Regional Burn Treatment Center use of cultured epithelial autografts (CEA) in patients with massive burn injuries
- Rapid, quantitative PCR-based detection of MRSA in burn sepsis patients (a project with the University of California-Davis funded by the American Burn Association Multi-Center Trials Group)
- A retrospective study determining the incidence and treatment of intra-abdominal hypertension / abdominal compartment syndrome in a burn treatment center
- The Burn Experiences Study: Understanding the recovery process after thermal burn injury (a project with the University of North Carolina's TRYUMPH Research Group)
- A comparison of the Nova Stat Strip blood glucose testing system to the clinical laboratory blood glucose determinations with focus on hemoglobin levels
- Rapid assessment of acute illness and injury to enhance the U.S. response to public health emergencies. (Multicenter project with the USCIITG-Prep Burn Group-completed January 2013)

Poster Presentations-American Burn Association Annual Meeting 2013

157. Patton, M.L., Haith, L.R., Ackerman, B.H., Reigart, C.L., Stair-Buchmann, M.E., Guilday, R.E. Transfusion Triggers in Burn Patients-A Retrospective Review.

164. Ackerman, B.H., Haith, L.R., Patton, M.L., Guilday, R.E., Reigart, C.L., Stair-Buchmann, M.E. Comparison of Serum Vancomycin Peak and Trough Concentration-Based Pharmacokinetic Parameters versus Those Derived Creatinine Clearance and Patient Weight.

248. Haith, L.R., Ackerman, B.H., Reigart, C.L., Stair-Buchmann, M.E., Guilday, R.E., Patton, M.L., Ross, K., Stoering, M. Evaluation of Aquacel Ag for Autogenous Skin Donor Sites.

Poster Presentation-International Society for Burn Injuries 2012

Haith, L.R., Patton, M.L., Guilday, R.E., Reigart, C.L., Stair-Buchmann, M.E., Young, C., Ravreby, W., Nelson, S., Ackerman, B.H. Evaluation of Nasal Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Polymerase Chain Reaction (PCR) as a Screening Tool for Prevention of Subsequent Infection.

Projects Submitted and/or Accepted for Publication FY 2012-2013

Orrey, D.C., Bortow, A.V., Hoskins, J.M., Shupp, J.W., Jones, S.W., Cicuto, B.J., Hwang, J., Jordan, M.H., Holmes, J.H., **Haith, L.R.**, Roane, B.M., Diatchenko, L., Cairns, B.A., McLean, S.A. (2012). Catechol-O-Methyltransferase Genotype predicts pain severity in hospitalized burn patients. *Journal of Burn Care and Research*, 33(4), 518-523.

Haith, L.R., Santavasi, W., Shapiro, T.K., Reigart, C.L., Patton M.L., Guilday, R.E., Ackerman, B.H. (2012). Burn center management of operating room fires. *Journal of Burn Care and Research*, 33(5), 649-653.

Ackerman, B.H., Patton, M.L., Guilday, R.E., Haith, L.R., Stair-Buchmann, M.E., Reigart, C.L. (2013). Trimethoprim-induced hyperkalemia in burn patients treated with intravenous or oral trimethoprim sulfamethoxazole for methicillin-resistant staphylococcus aureus and other infections: Nature or nurture? *Journal of Burn Care & Research*, 34(1), 127-132.

Ackerman, B.H., Guilday, R.E., Reigart, C.L., Patton, M.L., Haith, L.R. (2013). Evaluation of the relationship between elevated vancomycin trough concentrations and increased efficacy and/or toxicity. *Journal of Burn Care & Research*, 34(1), e1-e9.

Patton, M.L., Mullins, R.F., Smith, D., Korentager, R. (2013). An open, prospective, randomized, pilot investigation evaluating pain with the use of a soft silicone wound contact layer, Mepitel One vs. bridal veil and staples used on split-thickness skin grafts as a primary dressing. *Journal of Burn Care & Research*, POST COPYEDIT, 28 June 2013.

Ackerman, B.H., Haith, L.R., Patton, M.L., Guilday, R.E., Reigart, C.L., Stair-Buchmann, M.E. (2013). A comparison of clinical and microbiological efficacy of antibiotic regimens against acinetobacter baumannii. *Journal of Burn Care & Research*, 34(4), 403-412.

Ackerman, B.H., Reigart, C.L., Stair-Buchmann, M.E., Haith, L.R., Patton, M.L., Guilday, R.E. (2013). Use of nebulized antimicrobial agents in burned and mechanically ventilated patients with persistent acinetobacter baumannii, pseudomonas aeruginosa, or enterobacteriaceae. *Burns*, 39(5), 885-891.

Waldecker, S., Ackerman, B.H., Reigart, C.L., Haith, L.R., Patton, M.L., Guilday, R.E. (2013) Retrospective review of inhalation injury patients receiving APRV versus other ventilator modes for respiratory distress syndrome or acute lung injury in the Nathan Speare Regional Burn Treatment Center – submitted to *Burns* September 2013.

FY 2011-2012

Study 1 (Resuscitation Study)

We continue to screen every admission on a 24/7 basis with on-call coverage of the research team. During FY 2011-2012, a total of 512 patients were screened. 22 patients had a TBSA \geq 20%. 5 patients were enrolled. 2 patients completed the full 48 hours on the study. 3 patients did not complete the full 48 hours. 1-transferred to another hospital, 1-needed emergent CT scan, and 1-computer malfunction occurred. The other 17 patients with \geq 20% TBSA were excluded for a variety of reasons: 2-unable to obtain consent, 5-age, 4-didn't require CVC and/or foley, 2-went to OR within first 24 hours after injury, and 5-other.

On 5/18/2012, a computer and IV pump malfunction occurred during data collection on a patient and data may have been compromised. Several attempts were made at communicating with the Army computer engineer without success. As of 6/18/2012, there has been no response. There is a second computer and 2 other IV pumps to use until the others are repaired.

The strict inclusion criteria continued to be an issue with enrollment. The Crozer IRB required consent IN PERSON. After discussing the issue with the IRB several times, they agreed to allow us to obtain phone consent.

2 burn staff nurses became research certified and were educated on the process of obtaining consent and set-up of the fluid resuscitation equipment. This was done to cover the resuscitation study when no other research staff was available (ABA).

Study 2 (Donor Site Study)

Enrollment continues. A total of 512 patients were screened during FY 2011-2012. 13 patients were enrolled and 9 completed the study. Of the 4 who did not complete the study, 1-removed by research staff due to problems with the Aquacel Ag site (patient was still followed for the full course), 1-did not come to follow-up appointments, 1-enrolled prior to viewing wounds and wounds were only 78cm², and 1-didn't receive STSG in OR, just excision and VAC placement.

For the entire study period, a total of 30 patients have been enrolled. 23 patients have completed the study. In reviewing the paperwork, there are 3 patient charts that have too much data missing and will potentially be excluded and there are 4 patients that were withdrawn by research staff. We determined that a total of 7 patients will need to be replaced to meet the requirements of the study. To date 1 of these patients has been replaced, leaving 6 patients left to enroll.

IRB-Approved Projects FY 2011-2012

- Risk versus benefit of the addition of acetaminophen to oxycodone for pain management at the Nathan Speare Regional Burn Treatment Center
- Retrospective review of the experience of the Nathan Speare Regional Burn Treatment Center use of cultured epithelial autografts (CEA) in patients with massive burn injuries.
- Central venous catheter exchange strategies in patients with acute burn injury at Nathan Speare Regional Burn Treatment Center
- Comparison of instilled versus nebulized aminoglycosides in the treatment of tracheobronchitis associated with persisting endotracheal intubation in thermal injury patients
- Calciphylaxis management in a burn treatment center
- Stevens - Johnson syndrome and toxic epidermal necrolysis management in a burn treatment center
- Transfusion triggers in burn patients - A retrospective review

Oral Presentation-American Burn Association Annual Meeting 2012

An open, prospective randomized pilot investigation evaluating pain with the use of soft silicone wound contact layer, Mepitel® One, vs. Bridal Veil and staples used on split thickness skin grafts as a primary dressing.

Presented by Mary Lou Patton, MD (coordinating investigator), et al with Molnlycke® Healthcare

Poster Presentations-American Burn Association Annual Meeting 2012

Stair-Buchmann, M.E., Ackerman, B.H., Reigart, C.L., Guilday, R.E., Patton, M.L., Haith, L.R. Management of purpura fulminans in a burn treatment center. 44th Annual Meeting, American Burn Association, Seattle, WA April 23-27, 2012 (poster)

Stair-Buchmann, M.E., Ackerman, B.H., Reigart, C.L., Haith, L.R., Patton, M.L., Guilday, R.E. Pyoderma gangrenosum: A difficult diagnosis best managed in a burn treatment center. 44th Annual Meeting, American Burn Association, Seattle, WA April 23-27, 2012 (poster)

Ackerman, B.H., Patton, M.L., Guilday, R.E., Haith, L.R., Stair-Buchmann, M.E., Reigart, C.L. Trimethoprim-induced hyperkalemia in burn patients treated with intravenous or oral trimethoprim sulfamethoxazole for methicillin-resistant staphylococcus aureus and other infections: Nature or nurture? 44th Annual Meeting, American Burn Association, Seattle, WA April 23-27, 2012 (poster)

Ackerman, B.H., Guilday, R.E., Haith, L.R., Patton, M.L., Stair-Buchmann, M.E., Reigart, C.L. Impact of multiple drug resistant *acinetobacter baumannii* on changes in antibiotic susceptibility of *pseudomonas aeruginosa* in a burn treatment center. 44th Annual Meeting, American Burn Association, Seattle, WA April 23-27, 2012 (poster – won best in category)

Poster Presentation-Society of Critical Care Medicine Annual Congress 2012

Santavasi, W., Fitzpatrick, R.A., Haith, L.R., Ackerman, B.H., Stair-Buchmann, M.E., Herder, D., Reigart, C.L., Guilday, R.E., Patton, M.L. “Point of Care” glucose monitoring may be unreliable in critically ill burn patients with low hemoglobin. Presented at the Society of Critical Care Medicine's 41st Critical Care Congress, Feb. 2012, Houston, TX and also as the Keynote Address at the Crozer-Keystone Health System's Annual Nursing Research Symposium, Oct. 2011.

Poster Presentation-Surgical Infection Society 2012

Haith, L.R., Young, C., Ackerman, B.H., Reigart, C.L., Stair-Buchmann, M.E., Patton, M.L., Guilday, R.E., Ravreby, W.D., Nelson, S.C. Evaluation of methicillin-resistant *Staphylococcus aureus* (MRSA) Polymerase Chain

Reaction (PCR) as a screening tool in burn center patients. Annual Meeting of the Surgical Infection Society of North America, Dallas, TX, April 14, 2012 (poster).

Projects Submitted for IRB Approval FY 2011-2012

- Rapid, quantitative PCR-based detection of MRSA in burn sepsis patients (a project with the University of California-Davis funded by the American Burn Association Multi-Center Trials Group)
- A retrospective study determining the incidence and treatment of intra-abdominal hypertension / abdominal compartment syndrome in a burn treatment center
- The Burn Experiences Study: Understanding the recovery process after thermal burn injury (a project with the University of North Carolina's TRYUMPH Research Group)
- A Comparison of the Nova Stat Strip blood glucose testing system to the clinical laboratory blood glucose determinations with focus on hemoglobin levels

Projects Submitted and/or Accepted for Publication FY 2011-2012

- Trimethoprim-induced hyperkalemia in burn admission treated with intravenous or oral trimethoprim sulfamethoxazole
- A comparison of the Contour blood glucose testing system to the Accu-Chek® blood glucose testing system
- Retrospective review of inhalation injury patients receiving APRV versus other ventilator modes for respiratory distress syndrome or acute lung injury in the Nathan Speare Regional Burn Treatment Center
- Elimination of resistant *acinetobacter baumannii*: The success of a multidisciplinary task force

Santivasi, W.L., Kulkarni, S., Patton, M.L., Haith, L.R., Guilday, R.E., Reigart, C.L., Ackerman, B.E. (2011). Infiltration of sodium valproate with compartment syndrome and bullous reaction: Case report and literature review. *Burns*, 37(7), e59-e62.

Baetz, B.E., Patton, M.L., Guilday, R.E., Ackerman, B.H., Reigart, C.L. (2011). Amlodipine-induced toxic epidermal necrolysis. *Journal of Burn Care and Research*, 32(5), e158-e160.

Hornbeek, H., Haith, L.R., Ackerman, B.H., Stair-Buchmann, M.E., Patton, M.L., Guilday, R.E., MD, Reigart, C.L. (2012). Pseudoallecheria boydii infection of the brain. *Surgical Infections*, 13(3), 179-180. doi:10.1089/sur.2011.111.

FY 2010-2011

Study 1 (Resuscitation Study): During the period of this annual report until the site visit with the USAISR, the burn research team moved forward with educating the entire burn center staff on details of the resuscitation study. This included competencies on Alaris IV pumps, the AbViser and the urimeter equipment. Crozer engineers coordinated our monitoring equipment in preparation for connection to the DAQ computer. The research nurse continued to remain in on-call status (not billed to the grant). In August, 2010, USAISR notified us that they needed to upgrade the software design prior to the installation site visit. Crozer requested a 2-year contract time extension which was approved. In September and October, the USAISR engineers continued to upgrade the software. Finally, in November, 2010, an engineering site visit occurred. Two laptops were installed instead of one DAQ machine giving us added capacity to enroll patients. However, cables and the updated software were still not available. In December, we continued detailed education of the burn team on the study protocol details. The cables arrived, but not the software. In January, 2011, we began screening patients in anticipation of the software's imminent arrival. The burn research nurse went to full-time status on the grant on 1/31/2011. We continued screening (but not enrolling) patients and as of March 31, a total of 114 patients had been screened (note: only 5 of these 114 patients would have met the study criteria had the software been available). In April, 2011, the software upgrade (patch) was

received and the study was able to commence. An additional 34 patients were screened that month. One patient met criteria for the study, however, the computer and software did not function properly requiring intervention by the Army's engineer. Enrollment of this patient was delayed by this work, being enrolled at the 25.5 post injury hour mark (the protocol requires enrollment at 24 hours or less, however we continued data collection on this patient for 48 hours). By the end of April, 2011, both computers were fixed and functional. At the end of the report year (June, 2011), 240 patients had been screened, 2 patients were enrolled. To date, we have screened every admission on a 24/7 basis with on-call coverage of the research team.

The strict exclusion criteria for Study 1 which, among other exclusions, includes a requirement that the patient to be enrolled within 24 hours of injury, combined with the Crozer IRB requirement of obtaining informed consent directly from family members of the patient, have proven to be problematic to the study. In addition, with the trend to decrease the incidence of hospital acquired infections related to central lines, the use of peripheral IV lines for certain patients has become standard of care. This has put another barrier into meeting enrollment criteria for this study (which requires central lines and foley catheters). Several patients have also refused foley catheters. The study stipulates that the standard of care cannot be changed. We are making every effort to address these barriers in the coming year. However, we anticipate that due to the delays in start-up that were outside our control, we will have a need for a contract extension when it expires in July, 2012.

Study 2 (Donor Site Study): Enrollment of patients into this study began in April, 2009 and continued throughout this study year. A total of 480 patients were screened during this contract period (July, 2010 to June, 2011). During this time period, 8 patients were enrolled, bringing the total enrollment at the end of the period to 17. The Research Nurse makes daily rounds on the burn unit to identify possible candidates for the study. Due to the limits of the eligibility criteria, enrollment has been difficult. However, despite this, we anticipate no problems in achieving the study objectives in the coming year. A full internal audit of all data collected to date was completed. Several of the screening numbers have changed as a result of this audit.

Study 3: Study 3, a project defined by Crozer, has not begun because Crozer has not had any patients that met the criteria for inclusion since April, 2008. The study was focused on the poly-resistant *A. Baumannii*, which was eliminated in the burn unit in 2007 and has not recurred. In order to fully utilize the burn research nurse, we have worked on other projects applicable to the military theatre which have contributed to other areas of burn research. In the report period from July to January, 2011, we completed a project on the effects of low hemoglobin on bedside point of care glucose monitoring. These projects are summarized below.

IRB-Approved Projects FY 2010-2011

- Comparison of instilled versus nebulized aminoglycosides in the treatment of tracheobronchitis associated with persisting endotracheal intubation in thermal injury patients
- Relationship between nasal swab methicillin-resistant staphylococcus aureus (MRSA) PCR-positive test results and subsequent MRSA infection in thermal injury.

Presentations-American Burn Association Annual Meeting 2011

Ackerman, B.H., Guilday, R.E., Reigart, C.L., Patton, M.L., Haith, L.R. Evaluation of the Relationship between Elevated Vancomycin Trough Concentrations and Increased Efficacy and/or Toxicity (platform presentation)

Haith, L.R., Santavasi, W., Shapiro, T.K., Reigart, C.L., Patton, M.L., Guilday, R.E., Ackerman, B.H. Burn Center Management of Operating Room Fires. (poster)

Ackerman, B.H., Reigart, C.L., Stair-Buchmann, M.E., Haith, L.R., Guilday, R.E., Patton, M.L. Use of nebulized antimicrobial agents in burned and mechanically ventilated patients with persistent acinetobacter baumannii, pseudomonas aeruginosa, or enterobacteriaceae. (poster)

Presentation-Surgical Infection Society Annual Meeting 2011

Waldecker, S., Ackerman, B.H., Reigart, C.L., Haith, L.R., Patton, M.L., Guilday, R.E. Retrospective review of inhalation injury patients receiving APRV versus other ventilator modes for respiratory distress syndrome or acute lung injury in the Nathan Speare Regional Burn Treatment Center

Accepted for American Burn Association Annual Meeting 2012

- Management of purpura fulminans in a burn treatment center
- Pyoderma gangrenosum in a burn treatment center
- Trimethoprim-induced hyperkalemia in burn admissions treated with intravenous or oral trimethoprim sulfamethoxazole
- Impact of multiple drug resistant (MDR) *Acinetobacter baumannii* on changes in antibiotic susceptibility of *Pseudomonas aeruginosa*

Accepted for Society of Critical Care Medicine Annual Congress 2011

- Point of care glucose monitoring may be unreliable in critically ill burn patients with low hemoglobin

Submitted to Surgical Infection Society for 2012 Annual Meeting

- Relationship between nasal swab methicillin-resistant staphylococcus aureus (MRSA) PCR-positive test results and subsequent MRSA infection in thermal injury

FY 2009-2010

Presentations-Surgical Infection Society Annual Meeting 2010

Haith, L.R., Ackerman, B.H., Hornbeek, H., Patton, M.L., Guilday, R.E.: *Scydosporium* Brain Abscesses in a Patient with a Patent Foramen Ovale Caused by Sinusitis and Fungal Pneumonia Following a Work-Related Boiler Explosion. Presented at the 30th Annual Meeting of the Surgical Infection Society, Las Vegas, Nevada, April 17-20, 2010. (poster)

Haith, L.R., Guilday, R.E., Okechukwu, C.N., Patton, M.L., Neeli, S., Poldolsky, E.: Calcific Uremic Arteriopathy-A Combined Aggressive Conjoint Nephrology/Burn Surgery Management. Presented at the 30th Annual Meeting of the Surgical Infection Society, Las Vegas, Nevada, April 17-20, 2010. (poster)

Ackerman, B.H., Phillips, K., Guilday, R.E., Patton, M.L., Haith, L.R.: Is There a Relationship Between Elevated Vancomycin Trough Concentrations (VT) and Increased Efficacy or Toxicity? Presented at the 30th Annual Meeting of the Surgical Infection Society, Las Vegas, Nevada, April 17-20, 2010. (poster)

Reigart, C.L., Ackerman, B.H., Adams, P., Young, C., Guilday, R.E., Patton, M.L., Haith, L.R., Ravreby, W.D.: Multidisciplinary Performance Improvement (PI) Task Force Project Markedly Reduced and Eliminated Resistant *Acinetobacter Baumannii*/Haemolyticus (AB). Presented at the 30th Annual Meeting of the Surgical Infection Society, Las Vegas, Nevada, April 17-20, 2010. (poster)

Ackerman, B.H., Adams, P., Young, C., Reigart, C.L., Guilday, R.E., Patton, M.L., Haith, L.R., Ravreby, W.D.: Assessment of the Treatment of *Acinetobacter Baumannii* Following the Outbreak of a Multi-resistant Clone and a Variant Clone in a Burn Treatment Center. Presented at the 30th Annual Meeting of the Surgical Infection Society, Las Vegas, Nevada, April 17-20, 2010. (poster)

Projects Submitted and/or Accepted for Publication FY 2009-2010

Galler, A.S., Patton, M.L.: Extravasation of contrast material in anterior chest wall: Case report and literature review. *ScienceDirect – Injury Extra*. Feb, 2010: Volume 41, 17-19.

Klein, J.M., Hoffman, C., Relaxation and Visual Imagery Techniques: Do They Work? Can They Really Help Burn Patient? *MedSurg Nursing*. May/June 2010; Volume 19: No.3.

REPORTABLE OUTCOMES:

Study 1-Automated Fluid Resuscitation of Burn Patients

Specific Aims/Significance:

1. Data collection in Phase I is the first step in developing full “closed-loop” resuscitation that automatically titrates fluid therapy to changes in urinary output.

Outcome: Data was collected as per the protocol.

2. The study will allow testing of the robustness of the monitoring system and how well it works as a data acquisition system under actual patient care conditions.

Outcome: Data was collected as per the protocol. When it was fully functional, the computer system ran independently once set up by research staff and only required a “quick look” at the screen to determine that data was being collected. Assessment of actual data collected will be determined by the Army engineer extracting the data. The project clearly identified limitations of the computer monitoring system under actual patient conditions which will benefit future phases of the research.

The U.S. Army Institute for Surgical Research has received all data related to the Automated Fluid Resuscitation of Burn Patients and will be performing data analysis in preparation for publication. We were unable to complete the full course of the study due to computer malfunctions and barriers to obtaining consent.

Study 2-Evaluation of Aquacel Ag Dressing for Autogenous Skin Donor Sites

Specific Aims:

1. Pain as perceived by the patient will be equal or less with the Aquacel Ag dressing compared to Xeroform.

Outcome: Although donor sites treated with Xeroform received higher daily pain scores initially, as the study course progressed, patients gave higher pain scores to the donor sites treated with Aquacel Ag. When asked about overall comfort, more patients preferred Xeroform. Most patients stated that the hardening of the Aquacel Ag over time resulted in more pain.

2. The cosmetic effect of healing at post surgery day 30-45 will be equal to or greater with the Aquacel Ag compared with the Xeroform.

Outcome: Vancouver Scar Scores between the 2 donor sites were not statistically significant. In the blinded photo review, cosmesis was noted to be better in the Xeroform site though the photo reviewer could not see a difference in the 2 donor sites in a majority of the subjects.

The Evaluation of Aquacel Ag Dressing for Autogenous Skin Donor Sites study has been completed. Preliminary data was presented in poster form at the 2013 American Burn Association’s Annual Meeting. Currently, the manuscript is being written which we plan to submit to the Journal of Burn Care and Research for publication.

CONCLUSION:

Study 1-Automated Fluid Resuscitation of Burn Patients

This study was conducted to assist the military in testing the decision support system as the first step in developing a full “closed-loop” resuscitation system that will automatically titrate fluid therapy to changes in urinary output. This would benefit medical personnel in mass casualty scenarios in civilian and military populations and those treating individual patients with large burns in burn centers.

Initiation of the study was time consuming and labor intensive, but once up and running, the DAQ computer system functioned and data was collected. Within one year of study initiation, equipment malfunctions began to occur and extensive communication with the Army engineer, PI, and our internal IS department took place in attempts to rectify the issues. The current software was being updated and validated and we would need to update our equipment once the validation was complete. We never received the updated software. Despite these problems, we continued to screen and enroll patients in the study. A total of 11 patients were enrolled with 10 having varying degrees of data collected.

Through the course of the study, we found that staff tended to pay closer attention to resuscitation efforts when a patient was enrolled in the study. The use of the Ab-Viser was a welcome addition to our monitoring procedures and we are in the process of bringing the product into our hospital for use on all of our patients with larger burns. The urimeter received mixed responses from the nursing staff. The need to add the every 10 minute urine outputs together every hour was tedious, but the digital system gave more accurate urine output measurements. The monitoring system “ran” itself requiring very little intervention by research staff. A quick look at the monitor screen and we were able to determine if everything was functioning. The equipment took up a good amount of space at the bedside and could not travel with the patient, so a smaller, more compact system would be beneficial in the future.

The Crozer IRB was a barrier to successful enrollment of patients in this study. Despite the fact that this was only an observational study, our IRB required consent for participation. Initially, consent was required in person, which severely limited our ability to obtain consent, especially when a good portion of our patient population comes from a 4-state area. Eventually, the IRB agreed to telephone consent, which did allow us to obtain consent on 2 patients. Telephone consent had its barriers as well, with family members not returning phone calls.

Enrollment was also affected by study criteria, mostly the requirement of a central line. We found that many of our patients were admitted with peripheral lines and did not require a central line until after the 24 hour post-burn time frame. We made sure that we did not insert central lines expressly for the purpose of the study as this was not part of the consent.

Improper fluid resuscitation in our burn center continues to be an issue. With all of the current research, continued improvements need to be made to our resuscitation protocol. To accomplish this, we would need to do further research on our resuscitation efforts and develop a new resuscitation algorithm. In the future, we would like the opportunity to participate in a similar study, but would consider amending the consent to allow for central line placement for the purpose of the study and telephone consent. We hope that this information further assists the military in developing a “closed-loop” resuscitation system.

Study 2-Evaluation of Aquacel Ag Dressing for Autogenous Skin Donor Sites

The Evaluation of Aquacel Ag Dressing for Autogenous Skin Donor Sites study was a success for our burn center even though it took 4 years to complete enrollment. The inclusion criteria were very strict so that the results would be applicable to the military. Our burn center sees approximately 450-500 patients per year, but very few met criteria for the study. The most common reasons for exclusion were patients that did not receive skin grafting, pediatric patients, and those with non-burn skin disorders.

A total of 34 patients were enrolled, with 29 completing the full study course, 17 males and 12 females. The average age of our patients was 41 with an average TBSA of 10%. Five patients were removed from the study for a variety of reasons: 1 patient did not end up requiring STSG, 1 patient became mentally unstable, 1 patient only agreed to participate if both donor sites could be on the same thigh, but this was not deemed feasible once the

wounds were measured in the OR, 1 patient's donor site only measured out to be 78cm², and 1 patient was scheduled for STSG, but only received excision and vacuum-assisting wound closure.

Donor sites treated with Xeroform re-epithelialized faster than those treated with Aquacel Ag. These data may be mildly skewed as some patients' dressings fell off while at home and they were unable to give an exact occurrence date. Days to 90% re-epithelialization was recorded as the date on which research staff noted 90% re-epithelialization in the burn clinic, unless the patient gave the exact occurrence date. Three potential wound infections occurred in the Aquacel Ag donor sites. Donor sites were documented as infected if they displayed warmth, erythema, increased pain, increased skin temperature, or purulent drainage and antibiotics were prescribed. All 3 patients were treated with antibiotics and the donor sites healed without further issues.

Xeroform daily pain scores averaged higher than Aquacel Ag, but when it came to comfort, the patients were more likely to rate Xeroform as more comfortable or they were unable to discern a difference between the two sites. This was more evident later in the course of healing possibly as a result of hardening of the Aquacel Ag. Many of the patients tended to complain of more discomfort and decreased range of motion as the Aquacel Ag dried and hardened. In 2 patients, the Aquacel Ag was removed due to severely impaired range of motion. Removal of dried and hardened Aquacel Ag proved difficult, even when soaked with saline and Keri Oil. Vancouver Scar Scores between the 2 donor sites were not statistically significant. In the blinded photo review, cosmesis was noted to be better in the Xeroform site though the photo reviewer could not see a difference in the 2 donor sites in a majority of the subjects.

We continue to use Xeroform on donor sites as well as several other products. Aquacel Ag is not in use in our burn center at this time. At the onset of the study, we used Aquacel Ag for partial thickness burns and some non-burn skin disorders. Over time and through the course of the study, we found that Aquacel Ag was more difficult to deal with and more uncomfortable for the patients, so it was eventually phased out of our wound care routine.

We would like to continue to search for the most beneficial donor site product for our patients. In the future, we plan to do another comparison study on donor site dressings.

REFERENCES: None

APPENDICES: Journal publications, journal submissions, and presentations attached.

SUPPORTING DATA: None

LIST OF PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT:

- Linwood R. Haith, Jr., MD, FACS, FCCM
- Megan E. Stair-Buchmann, RN, BSN
- Bruce H. Ackerman, PharmD
- Cynthia L. Reigart, RN, BSN
- Diane Herder, RN

LIST OF APPENDICES

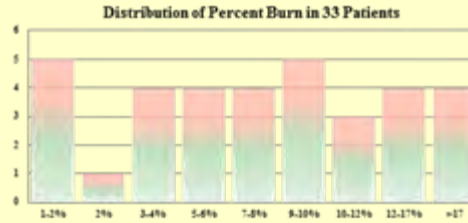
1. "Evaluation of Acquacel Ag for Autogenous Skin Donor Sites" (poster)
2. "Impact of multiple drug resistant (MDR) Acinetobacter baumannii (AB) on changes in antibiotic susceptibility of Pseudomonas aeruginosa (PA) in a Burn Treatment Center" (poster)
3. "A Comparison of Clinical and Microbiological Efficacy of Antibiotic Regimens Against Acinetobacter baumannii" (JBCR)
4. "Multidisciplinary Performance Improvement (PI) Task Force Project Markedly Reduced and Eliminated Resistant Acinetobacter Baumannii/Haemolyticus (AB)" (poster)
5. "Assessment of the Treatment of Acinetobacter Baumannii Following the Outbreak of a Multi-Resistant Clone and a Variant Clone in a Burn Treatment Center" (poster)
6. "Amlodipine-Induced Toxic Epidermal Necrolysis (TEN)" (JBCR)
7. "Retrospective Review of Inhalation Injury Patients Receiving APRV versus other Ventilator Modes for Respiratory Distress Syndrome or Acute Lung Inhalation in the Nathan Speare Regional Burn Treatment Center" (pending review for publication in Burns)
8. "Evaluation of nasal methicillin-resistant Staphylococcus aureus (MRSA) Polymerase Chain Reaction as a screening tool for prevention of subsequent infection" (poster)
9. "Calcific Uremic Arteriopathy-A Combined Aggressive Conjoint Nephrology/Burn Surgery Management" (poster)
10. Catechol-O-Methyltransferase (COMT) Genotype Predicts Pain Severity in Hospitalized Burn Patients" (JBCR)
11. "Extravasation of contrast material in anterior chest wall: Case report and literature review" (Burns)
12. "Evaluation of Burn Center Patients with Hemoglobin Concentrations Below 7.0g/dL" (poster)
13. "Hyperkalemia Associated with Treatment of Thermal Injury Patients with Oral Sulfamethoxazole and Trimethoprim (T/S)" (poster)
14. "Infiltration of sodium valproate with compartment syndrome and bullous reaction: Case report and literature review" (Burns)
15. "An Open, Prospective, Randomized Pilot Investigation Evaluating Pain With the Use of a Soft Silicone Wound Contact Layer vs. Bridal Veil and Staples on Split Thickness Skin Grafts as a Primary Dressing" (Mepitel One) (JBCR)
16. "Pyoderma Gangrenosum: A Difficult Diagnosis Best Managed in a Burn Treatment Center" (poster)
17. "Burn Center Management of Operating Room Fire Injuries" (JBCR)
18. "Use of nebulized antimicrobial agents in burned and mechanically ventilated patients with persistent Acinetobacter baumannii, Pseudomonas aeruginosa, or Enterobacteriaceae" (Burn)
19. "Pseudallescheria boydii Infection of the Brain" (Surg Inf)
20. "Point of Care glucose monitoring may be unreliable in critically ill burn patients with low hemoglobin" (poster)
21. "Management of Purpura Fulminans in a Burn Treatment Center" (poster)
22. "Is There a Relationship Between Elevated Vancomycin Trough Concentrations and Increased Efficacy or Toxicity?" (poster)
23. "Evaluation of the Relationship Between Elevated Vancomycin Trough Concentrations and Increased Efficacy and/or Toxicity" (JBCR)
24. "Scediosporium Brain Abscesses in a Patient with a Patent Foramen Ovale Caused by Sinusitis and Fungal Pneumonia Following a Work-Related Boiler Explosion" (poster)
25. "Trimethoprim-Induced Hyperkalemia in Burn Patients Treated with Intravenous or Oral Trimethoprim Sulfamethoxazole for Methicillin-Resistant Staphylococcus aureus and Other Infections: Nature or Nurture?" (JBCR)
26. "Comparison of Serum Vancomycin Peak and Trough Concentration-Based Pharmacokinetic Parameters Versus Those Derived Creatinine Clearance and Patient Weight" (poster)

Introduction

Burn wounds and other soft tissue injuries requiring skin grafts are increasingly common occurrences among both the military and general population. An ongoing objective of soft tissue trauma and burn research is to evaluate various wound dressings and to develop new treatments to expedite wound healing. This was a single-center, prospective, randomized and controlled study to evaluate the effectiveness of Aquacel Ag (AA) for the use as a dressing for autogenous skin donor sites compared to Xeroform (XF), which was our standard treatment at the onset of this study. We hypothesized that the mean healing time for wounds treated with Aquacel Ag would be less than the mean healing time for wounds treated with Xeroform.

Materials and Methods

- From March 2009 – March 2013 all patients admitted to the burn center were screened for enrollment.
- Inclusion Criteria:
 - Age > 18 years of age
 - TBSA < 30%
 - No history of IDDM, peripheral vascular disease, or clotting disorders
 - Need for STSG requiring $\geq 100\text{cm}^2$ donor site skin
 - English-speaking
 - Non-ventilated
 - Of sound mind and able to understand and sign consent
- 2 separate donor sites of similar size were required
- Donor sites were harvested at a depth of 10/1000th of an inch
- Epinephrine 1:1,000,000 solution was injected into each donor site prior to harvesting
- Aquacel Ag was applied to the donor site to the patients' right & Xeroform to the donor site to the patients' left
- Wounds were assessed daily beginning on post-op day #2 and continued until discharge.
- Daily assessments documented pain, overall comfort, signs of infection, and any replacement or trimming of dressings.
- Patients were then followed in the outpatient burn clinic until post-op day 30-45.
- Photographs were taken of the donor sites on post-op day #2, day of 90% re-epithelialization, and between post-op day 30 and 45.
- Scar assessments and blinded photo reviews were also completed to evaluate cosmetic outcome.



Results

33 (21 male and 12 female) patients were enrolled¹ and 28 had evaluable data (See Table 1). Re-epithelialization occurred more rapidly and daily pain scores were higher with Xeroform (See Table 1). Aquacel Ag needed to be replaced more often than Xeroform (1.8x vs. 0.11x) and was more comfortable for an average of 2.6 days vs. 2.5 days for Xeroform.

Patients tended to prefer Aquacel Ag earlier in the course of healing, but as it hardened, it became more intolerable. In 2 cases, Aquacel Ag impeded range of motion as it hardened and had to be removed. Aquacel Ag performed better when applied to the medial thigh rather than the lateral thigh. When applied to the lateral thigh, it tended to become "soupy" and slide off, especially in patients of larger size. Infections occurred in the Aquacel Ag donor site in 2 patients

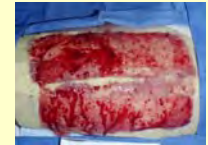
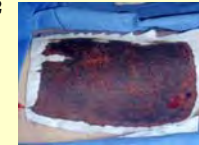
On average, Vancouver scar scores were 2.5 for Xeroform & 2.8 for Aquacel Ag. The blinded photo review concluded that Xeroform had a better cosmetic outcome 23% of the time vs. 0.07% with Aquacel Ag. 69.2% of the time the reviewer was unable to determine a cosmetic difference between the 2 sites.

Table 1. Demographic Data and Paired Donor Site Dressing Comparison

	AGE	% TBSA	Days to 90% AA	Days to 90% XF	Days Pain AA	Days Pain XF	Scar S AA	Scar S XF
Median	43	7.25	17	13.5	5	6.25	2.8	2.5
IQ range	(31-52)	(4-12)	(13-22)	(12-19)	(4-7)	(4.75-8)	(1-3)	(2-3.44)
T-test	--	--	3.424		1.153		1.449	
P	--	--	<<0.05		NS		NS	

Aquacel Ag Xeroform

POD #2



90% Re-epithelialization



POD #30-45



Right Thigh

Left thigh

Conclusion:

Xeroform demonstrated shorter healing times & better cosmetic outcomes than Aquacel Ag. Although the average daily pain scores for Aquacel Ag were lower than Xeroform, the patients tended to complain of more pain in the Aquacel Ag site as it hardened, later in the course of healing. The only 2 donor site infections occurred with Aquacel Ag.

¹Patient number 34 was enrolled in the study during the development of this poster and has not completed the full study course at this time. Data was not included.

ABSTRACT

INTRODUCTION: The transmission of resistance genes from one MDR organism to a potentially more virulent organism is worrisome. Following eradication of 2 clones of MDR *AB* in 2007, there was concern that MDR genes were transferred to *PA*. *PA* isolates from admissions to our burn center between 1999 and 2010 were reviewed with this focus.

MATERIALS AND METHODS: This IRB approved retrospective study identified 233 patients with at least one isolate of *PA* during their admission. The year, type of culture, number of cultures, antimicrobial agents selected, duration of antimicrobial therapy, changes in antimicrobial therapy due to emerging resistance, and exposure to MDR *AB* were recorded. Data were stratified by age, percent total body surface area involvement (TBSA), creatinine clearance, and survival status. Data were analyzed using students' t-test, ANOVA and nonparametric tests with X-square analysis for categorical data.

RESULTS: *PA* isolates from 1999 through 2010 were reviewed. Data were incomplete for 13 patients leaving 230 evaluable patients (96%). Mean \pm standard deviation data for age (49.3 \pm 20 years) and TBSA (25.3 \pm 23.0%). Survival status was significant for advanced age (T = 2.83; P <<0.05) and TBSA (T = 2.087; p <0.05). *AB* and *PA* caused co-infections in 65 patients (20%). No significant difference in patient demographics, ISS score, burn survival probability, ventilator support days, duration of first antimicrobial therapy, days prior to isolation of *PA* or length of stay (LOS) was noted. Survival for *PA* patients was 83.9% and for *PA* plus *AB* 89.2%. Number of positive cultures for sputum, central catheters, blood, urine, wounds and total cultures were not statistically different between groups indicating comparability. Analysis demonstrated changes in *PA* susceptibility in 145 of 1672 (8.6%) isolates from enrolled patients. The *AB* plus *PA* subset had 37 of 65 patients with 683 isolates with susceptibility pattern like the 2 clones of *AB* representing 40% of all *PA* isolates.

DISCUSSION: For nearly identical patient populations, the number of *PA* plus *AB* patients remained less than the *PA* only infected patients each year. This indicated that *PA* might be more virulent or more capable of colonizing burn patients than *AB*. Resistance genes from *AB* demonstrated temporary residence in 8.7% of *PA* plus *AB* patients but this was not sustained following the 2007 eradication of *AB*.

INTRODUCTION

PA remains a serious intensive care unit multiple drug resistant organism (MDRO).¹⁻³ *AB*, a formerly resident MDRO in our burn unit transferred resistance genes to *PA* and *Enterobacter* species. These two 'modified' MDRO's were not able to take permanent residence in the burn unit. *PA* has resistance genes that inactivate antimicrobial agents⁴ and limit entry of nutrients and antimicrobial agents via porin closure and "efflux pumps."⁵ Pneumonia, urinary tract infections, and wounds were the most common *PA* infections in our burn unit. Synergistic combinations, though recommended by the manufacturers of the antimicrobial agents commonly used, failed to demonstrate any added efficacy. The evaluation of the efficacy of imipenem cilistatin, piperacillin tazobactam, and aminoglycosides in *PA* infected patients following this apparent gene transfer was our goal.

METHODS AND MATERIALS

Between 1999 and 2010 our microbiology laboratory identified 233 burn patients with positive *PA* cultures. Patients were stratified into two groups: those with prior or concurrent *AB* infection and those with no documented *AB* infection. Patients were also stratified by single or multiple isolations of *PA*. Culture data were analyzed for changes in antibiotic (ABX) susceptibility as well as the number of positive cultures. Repeated cultures within 24 hours of the same site were counted as a single event. Numbers of *PA* isolates demonstrating changes in susceptibility consistent with gene transfer were counted as well as whether they persisted in subsequent cultures. Patient data were analyzed using students' t-test, ANOVA, and Chi-square as was appropriate for the data seeking a p-value of < 0.05 for significance.

Pseudomonas Infection Demographic Data				
	Age	Burn Size	LOS	Number of cultures
ALL Cx (n = 220 Pt)	50.2 \pm 20.2	26.9 \pm 23.0	54.1 \pm 37.5	1565
SCx (n = 119 Pt)	50.6 \pm 20.1	28.0 \pm 23.1	58.3 \pm 34.3	646
CVCx (n = 38 Pt)	51.1 \pm 21.3	38.3 \pm 24.0	63.8 \pm 35.9	80
BCx (n = 59 Pt)	48.2 \pm 20.5	34.5 \pm 25.8	57.9 \pm 45.3	106
UCx (n = 38 Pt)	57.2 \pm 20.5	32.5 \pm 24.6	76.8 \pm 50.1	73
WCx (n = 131 Pt)	50.1 \pm 20.7	29.4 \pm 23.0	57.3 \pm 39.3	660
	NS	NS	NS	

RESULTS

PA was isolated from 233 patients of which 220 had complete data. Culture data were stratified by site: sputum (SCx) (5.4 \pm 4.7 Cx/Patient), central venous catheter (CVCx) (2.1 \pm 2.4 Cx/Patient), blood (BCx) (1.9 \pm 1.2 Cx/Patient), urine (UCx) (1.9 \pm 1.2 Cx/Patient), and wound (WCx) (5.0 \pm 7.5 Cx/Patient). There was no significant difference in demographics (see table above). No pattern of *PA* isolation between sites was demonstrable (range 8 to 50 patients/year). Survival correlated with age (T = 3.21; p <0.05) as expected, but burn size did not. Stratification by *AB* co-infection (n = 65 patients) demonstrated no difference in age, renal function, burn size, or survival probability (F = 1.20; p >0.05). Stratification by TBSA (CLCR) noted as expected reduced CLCR with increasing age (F = 15.20; p <<0.05). Ventilator days were distributed over CLCR groups (F = 1.40; p >0.05) as was ventilator days and LOS. Patients with *AB* co-infection had a longer LOS; 43.7 \pm 31.0 versus 59.7 \pm 44.4 days (T = 2.15; p = 0.03). Susceptibility to ABX was noted in 145 of 1672 cultures and 37 of 65 *AB* co-infected noted changed susceptibility over time. A total of 683 *PA* isolates had reduced susceptibility to ABX over time. *AB* co-infection may explain the failure of these two Gram-negative bacteria to take residence in our burn unit when compared to patients with *PA* infections.

CONCLUSIONS

Both *AB* and *PA* are non-fermentors known to exchange plasmids and transposons with other Gram-negative bacteria. Both *PA* and *Enterobacter* species accepted resistance genes from *AB*, but the presence of clones containing these genes was not evident. Plasmids and transposons have specific requirements for which a bacteria may initially accept genes, but the "foreign-ness" of the genes may prevent their integration. Either incomplete compatibility or easier eradication of *PA* and *Enterobacter* species may explain the failure of these two Gram-negative bacteria to take residence in our burn unit.

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A Comparison of Clinical and Microbiological Efficacy of Antibiotic Regimens Against *Acinetobacter baumannii*

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Acinetobacter baumannii represents a cunning pathogen with multiple resistance genes. The authors report their experience with the treatment of two multiple drug-resistant *A. baumannii* clones. At least one positive culture was noted in 359 patients and, 323 had sufficient data for analysis. Of these, 42 patients were colonized leaving 281 antibiotic-treated infected patients. The average age was 48.1 ± 20.6 years (mean \pm standard deviation), total body burn surface area involvement (TBSA) was $30.8 \pm 25\%$. Inhalation injury was confirmed by bronchoscopy in 238 of 323 (74%) patients. The day to the first *A. baumannii* culture was 7.9 ± 8.9 and 6.5 ± 8.8 days for the colonized and infected patients, respectively. Survival to discharge was 95.4% for colonized patients and 77.1% for infected patients. A total of 1425 sputum cultures, 123 catheter cultures from 40 patients, 1130 blood cultures from 176 patients, and 1925 wound cultures were obtained from the 318 infected patients (14 cultures per patient). Imipenem-cilastatin was first used in 162 patients, ampicillin-sulbactam in 40 patients, and cephalosporin in 41 patients. Imipenem-cilastatin was combined with ampicillin-sulbactam in 18 patients. Imipenem-cilastatin eradicated *A. baumannii* in 27%, caused persistence in 55%, and failure in 20%. Ampicillin-sulbactam eradicated *A. baumannii* in 17%, caused persistence in 51%, and failure in 34%. Imipenem-cilastatin combined with ampicillin-sulbactam eradicated 23% of the *A. baumannii*, with 54% persisting, and 23% failing therapy. Nonparametric analysis of three sets of 34 matched patients treated with imipenem-cilastatin, ampicillin-sulbactam, or a cephalosporin showed little difference in treatment outcomes. More rapid fever resolution and fewer positive cultures were noted in the imipenem-cilastatin treated group; however, length of stay was not different. (J Burn Care Res 2013;34:403-412)

The treatment of *Acinetobacter baumannii* infections with currently available antimicrobial agents has been based on small- to moderate-sized studies.¹⁻⁴ These studies provided no criteria for distinguishing colonized from infected patients.^{3,5,6} Synergistic combinations of antimicrobial agents against *A. baumannii* have been tried with variable success.^{1,7-11} Standard

antimicrobial agent doses against multiple drug-resistant organisms (MDROs) may be inadequate in critical care patients.¹²⁻¹⁵ Susceptibility testing with the MicroscanWalkaway System (Siemens Healthcare Diagnostics, Inc., West Sacramento, CA) poorly directed antimicrobial agent selection against this organism.^{1,9,12,16} Massive numbers of resistance genes and poor growth of *A. baumannii* in media compromise the speed and accuracy of specific antimicrobial agent susceptibility testing.¹⁶⁻¹⁸ The goal of this retrospective research was to assess *A. baumannii* experience with antimicrobial agents and to look for subtle or frank differences in outcome. This analysis was one of the tasks assigned to the Multidisciplinary Performance Improvement Burn Center Task Force evaluating *A. baumannii* infections in our burn center.

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An initial analysis of 150 patients indicated that high-dose imipenem-cilastatin at 1 g every 6 hours was more effective therapy than 6 g of ampicillin-sulbactam every 6 hours^{19,20}; however, slow response to this agent was arousing interest in colistin^{5,21} and tigecycline.²² Using standard assessment of infection response,^{2-4,23,24} we evaluated and compared these currently used agents between October 1999 and June 2007 at our burn treatment center.¹⁹ Pneumonia and wounds represented, by far, the most common *A. baumannii* infections at our burn treatment center.

MATERIALS AND METHODS

A retrospective IRB-approved study of our experience with *A. baumannii* infections from October 1999 to July 2007 used positive culture data from the clinical microbiology laboratory, the infection control department, and other sources.

Patients

Patients were identified from *A. baumannii* culture reports and reports from the infection control department. A total of 358 patients were identified with at least one positive *A. baumannii* culture. For 36 patients, insufficient medical record information was available (absent charts, partial charts, etc) and thus they were excluded from analysis, leaving 323 patients. Patients with only inhalation injury, patients with Stevens-Johnson-Toxic Epidermal Necrolysis, and other American Burn Association approved diagnoses were included. For 42 patients, *A. baumannii* isolation was truly colonization with no need for antibiotic therapy. Two hundred eighty-one patients with isolated *A. baumannii* needed treatment with antibiotics.

Patient Selection

Patient data were assessed for number of cultures and the number of days with persistence of *A. baumannii*. Coinfection with other organisms was also recorded. The patients were divided into two groups: colonized with *A. baumannii* and infected with *A. baumannii*.

Colonized With *A. baumannii*

Patients reported with single cultures of *A. baumannii* and patients reported to have *A. baumannii* on multiple cultures and who were not treated with an antibiotic with activity against *A. baumannii* were designated as colonized.

Infected With *A. baumannii*

Symptomatic patients with more than one positive *A. baumannii* culture treated with an antimicrobial agent were designated as infected. These patients were required to have *A. baumannii* from at least two culture sites or have persistence of *A. baumannii* on subsequent cultures from at least one of the same sites.

Assessment of Cultures

Cultures were obtained by the wound care team for areas suspicious for infections. Cultures of blood and urine were obtained routinely on Mondays, Wednesdays, and Fridays according to the patient care protocol. A limited number of *A. baumannii* urine cultures (five) were not included in the analysis. For intubated patients, sputum was collected using the same thrice weekly protocol. Additional blood, central venous catheter, urine, wound, and sputum cultures were obtained as clinically indicated. Sputum and wound cultures were assessed for the presence of white blood cells (WBCs). Multiple cultures from the same culture type (blood, central venous catheter, wound, or sputum) were counted as a single event. Cultures were obtained by protocol on Mondays, Wednesdays, and Fridays and as indicated for sudden changes in clinical status.

Choice of Antimicrobial Therapy

Specific antimicrobial therapy had been chosen at the discretion of the attending physician. Infectious diseases consultants provided additional guidance and suggestions. Susceptibility data from recent *A. baumannii* isolation guided the empiric use of antimicrobial agents while awaiting reports of susceptibility. Our *A. baumannii* isolates routinely demonstrated multiple drug-resistant (MDR) susceptibility patterns in more than 80% of our isolates. Most commonly, the *A. baumannii* susceptibility demonstrated resistance to all antimicrobial agents with a minimum inhibitory concentration (MIC) of >8 mg/L for imipenem-cilastatin, >8/32 for ampicillin-sulbactam, and >16 for amikacin. Susceptibility data including acquisition of MIC data was used to guide therapy and dose selection. These data were collected retrospectively. All patients were retrospectively assessed for potential differences in outcome by the Multidisciplinary Performance Improvement Burn Center Task Force. Imipenem-cilastatin was initiated at 1 g every 6 hours for patients with normal renal function (creatinine clearance >50 ml/min); ampicillin-sulbactam 6 g every 6 hours (creatinine clearance >50 ml/min); cefepime 2 g every 8 hours,

tigecycline 50 mg every 12 hours, or colistimethate at 5 mg/kg/day divided into every 8 to 12 hours regimens. Amikacin was used either as a 17 mg/kg/day in doses divided every 12 hours or as individualized once daily doses with targeted peak concentration goals of greater than five times the MIC. Doses were determined from the prescribing information for each antibiotic used and the average milligram per kilogram dose for patients with renal impairment (creatinine clearance < 50 ml/min) and normal renal function (creatinine clearance > 50 ml/min were recorded).

Patient Data and Assessment

Patient data for the colonized and infected patients included retrospective collection of routine laboratory tests, vital signs, culture results, and weight. Laboratory data included WBC count, differential of the WBC count, serum electrolytes, and serum creatinine. Smoking status, ethanol use, history of hypertension, diabetes, cardiac disease, and inhalation injury were also collected and used in demographic data analysis.

Criteria for Evaluation of Pulmonary Infections

Response to therapy was based on the Guidelines of the Infectious Diseases Society of America—American College of Chest Physicians which state that ventilator-associated pneumonia therapy should not exceed 21 days. Antimicrobial therapy was evaluated by persistence of cultures and signs and symptoms consistent with infection lasting more than 21 days.

Assessment of Renal Function

Creatinine clearance with correction for weight 1.25 or <0.85 of ideal body weight was used for calculation. Serum creatinine was not corrected to 1.0 for patients with serum creatinine <0.8 mg/dL. Patients were stratified for creatinine <25 ml/min, 25.1 to 50 ml/min, 50.1 to 100 ml/min, 100.1 to 125 ml/min, or >125.1 ml/min. Antibiotic doses were adjusted for renal function according to the manufacturer's recommendations for patients with renal impairment or in need of hemodialysis.

Clinical Evaluation of Response to Therapy

Patients dying of any cause during *A. baumannii* treatment were considered treatment failures. For those patients with preinfection clinical data, treatment period data were compared, and for those

patients with posttherapy data. Comparison of pre-treatment to antibiotic treatment was available for 121 patients (38%) to assess response to therapy. Persistence of cultures at week 2 and week 3 were evaluated to determine improvement or failure to meet the 21-day guideline goal of positive response.

Microbiological Evaluation

Microbiological "cure" was defined as the eradication of *A. baumannii* from the infection site. For patients with respiratory tract infections, persistence of *A. baumannii* from sputum with resolution of other signs and symptoms of infection were considered a "clinical cure." Patients with continued *A. baumannii* isolation, but some residual symptoms (eg, low grade fever without elevation of WBCs, or elevation of WBCs and no fever), had "persistence." New isolation of *A. baumannii* within 72 hours of completing an antibiotic course was considered a treatment "failure." New isolation of *A. baumannii* after 72 hours was considered "reinfection" and not a treatment failure.

Statistical Analysis

Continuous data were initially analyzed using students' *t*-test, analysis of variance (ANOVA), and for categorical data, χ^2 seeking a *P* value of ≤ 0.05 . For data failing to demonstrate normal distribution, such data were log transformed to "normalize" the distribution. Failure of log transformation to approximate normality resulted in the use of nonparametric tests. Three populations of patients from the three most commonly used antibiotic regimens based on age and TBSA involvement were used for post hoc analysis. Data for this subgroup were analyzed using ANOVA to assure the patients were comparable, and then this subset of data was subjected to the Kruskal-Wallis test comparing rank difference in antibiotic response.

RESULTS

Initial analysis separated the antibiotic-treated patients with positive *A. baumannii* cultures into 42 colonized patients and 281 infected patients. For five of the 42 colonized patients, repeated wound cultures were obtained from patients (average 0.81 cultures per patient). Repeated wound cultures were the only *A. baumannii* isolation in 45 of 281 infected patients with an average number of cultures of 3.9 cultures per patient. Outbreaks of *A. baumannii* isolation were episodic and not related to any specific time period (Figure 1) more than the

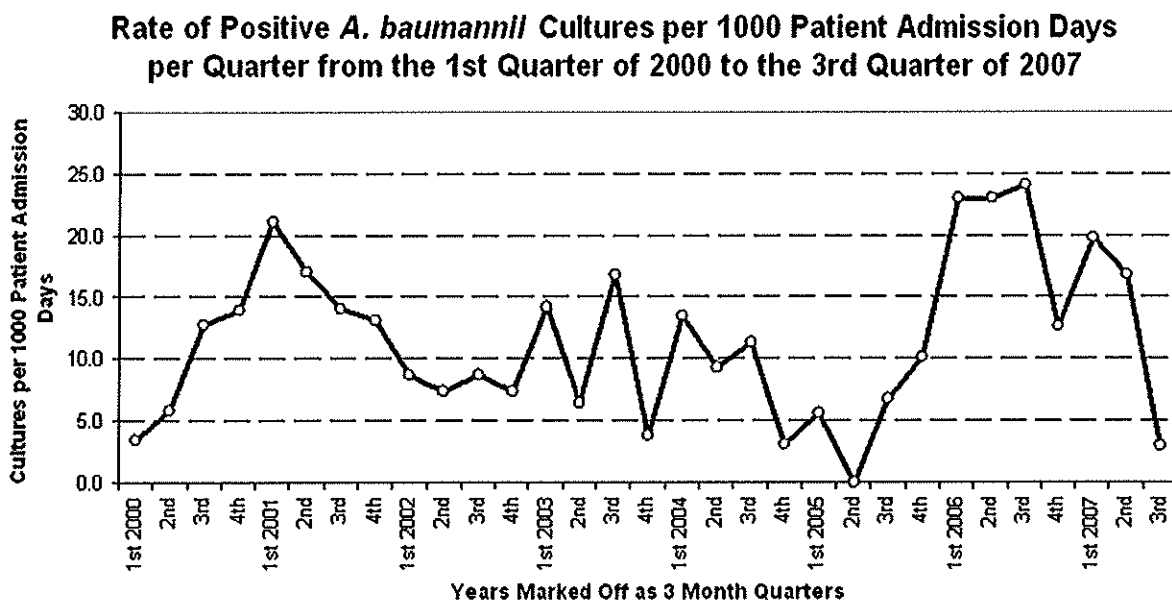


Figure 1. *Acinetobacter baumannii* outbreaks as per 1000 patient admission days from 2000 to 2007.

nearly 8-year period studied. Comparison of age, height, and weight were not statistically different ($T < 1$; NS) however; the percentage burn injury, the Injury Severity Score (ISS), and the survival probability (calculated from The Pennsylvania Outcome Performance Improvement Measurement System computer database) were all statistically different indicating as expected, the infected patients were "sicker." For 233 of the 281 infected patients, multiple sites of isolation were noted with more than one sputum, wound and central venous catheter, and blood culture ($N = 4593$), number of cultures averaged 16.5 per patient. t -Test comparison of the 42 colonized versus the 281 infected patients for age, height, weight, were not statistically significant. Ethanol detected at admission and inhalation injury was statistically more common in the infected patients with multiple sites of infection.

Patients

The colonized group represented 42 patients for which only a single *A. baumannii* culture had been isolated and five patients with multiple wound cultures for whom no antibiotic therapy was begun. Multiple cultures of *A. baumannii* in the 281 infected patients required treatment with antibiotics with known activity against *A. baumannii*. No significant difference was noted in age, days to *A. baumannii* colonization, survival probability, or renal function between colonized and infected patients. Patient demographic data are provided in Table 1.

Assessment of Cultures

A total of 4593 positive cultures representing an average of 16.5 (range: 4–21 culture isolates) separate cultures per infected patient were recorded for the 281 infected patients. A total of 1425 sputum cultures, 123 central venous catheter and 1130 blood cultures, and 1925 wound cultures were obtained from the 281 infected patients.

In spite of aggressive antimicrobial therapy, *A. baumannii* persisted beyond 21 days in approximately 40% of antibiotic-treated patients with multiple sites of infection. Thus pulmonary isolation of *A. baumannii* persisted beyond 21 days in 43% of patients with positive sputum cultures. Inhalation injury occurred in 223 of 281 (80%) of the infected patients.

Renal Function and Response

Antibiotic regimens were evaluated to determine if renal dysfunction correlated with treatment failure. Patient stratification was as defined above as creatinine <25 ml/min, 25.1 to 50 ml/min, 50.1 to 100 ml/min, 100.1 to 125 ml/min, or >125.1 ml/min (Table 2). Patient survival ranged from 66% for patients with creatinine clearance <50 ml/min to 94% in patients with creatinine clearance ≥ 125 ml/min. No significant difference in ISS score or length of stay (LOS) was noted for the patients stratified by renal function. Table 2 provides a stratified comparison of these patients. Chi-square analysis of the distribution of antimicrobial agents used for the four renal function strata did not differ ($\chi^2 = 30.98$; $P = .51$).

Table 1. Demographics of colonized and infected patients

	Age (years)	Height (cm)	Weight (kg)	TBSA (%)	Days to First AB Culture	LOS (days)
Demographics for 46 colonized patients (31 males 15 females) with 38 survivors (82.6%)						
Average	50.63	171.2	82.5	18.8	7.9	25.3
Standard deviation	19.62	17.7	24.7	21.0	8.9	22.4
Median	58	172.7	78.5	10.5	4.5	18
Intraquartile range	58–63	167.6–181.6	67.5–95.7	6.1–24.6	2.0–10.8	12–28
Kurtosis	-1.02	20.4	0.3	2.8	5.5	4.3
Skew	-0.11	-3.8	0.3	1.8	2.2	2.1
<i>t</i> -test	0.9425	0.5358	0.0332	3.390	0.9661	4.143
<i>P</i> value	NS*	NS	NS	<<.05	NS	<<.05
Demographics for infected patients (195 males; 123 females) with 255 survivors (80.2%)						
Average	48.1	169.7	82.4	30.8	6.5	41.4
Standard deviation	20.6	13.9	25.6	25.1	8.8	29.6
Median	46	170.2	79.8	25	4.0	33.5
Intraquartile range	34–63	165.5–179.5	65.7–96	10–46	2.0–8.0	19.3–56.0
Kurtosis	0.6	8.5	1.7	0.2	19.1	2.8
Skew	0.1	-2.1	0.8	0.9	3.8	1.4

*NS = Not significant

Table 2. Probability of survival scores and creatinine clearance of colonized and infected patients

	ISS Score	Survival Probability	Alternate Probability	Creatinine Clearance
Demographics for 46 colonized patients (31 males, 15 females) with 38 survivors (82.6%)				
Average	9.9	0.88	0.83	89.3
Standard Deviation	16.9	0.25	0.23	33.9
Median	6	0.97	0.90	89.3
Intraquartile Range	2.5–8.0	0.1–1.0	0.78–0.99	65.3–116.7
Kurtosis	-0.19	5.97	5.04	-0.7
Skew	0.71	-2.61	-2.22	-0.2
<i>t</i> -test	4.464	1.491	0.088	1.460
<i>P</i> value	<<.05	NS	NS	NS
Demographics for 318 infected patients (195 males; 123 females) with 255 survivors (80.2%)				
Average	20.9	0.81	0.83	81.3
Standard Deviation	14.7	0.25	0.21	31.7
Median	17	0.94	0.92	82.3
Intraquartile Range	9–32	0.72–0.99	0.72–0.98	59.5–103.4
Kurtosis	0.49	1.24	2.41	-0.4
Skew	0.84	-1.49	-1.63	-0.1

Antibiotic Therapy

Imipenem-cilastatin was used in 291 of 471 (62%) treatment courses in 162 treated patients. Ampicillin-sulbactam was used in 40 (14%) patients. Both imipenem-cilastatin and ampicillin-sulbactam were used concomitantly in 17 patients who were particularly ill. Cephalosporins (mostly cefepime with some ceftazidime use) were used as single agents in 41 patients with cellulitic wound cultures.

Fluoroquinolones were used as single agents in nine patients, aminoglycosides were used as single agent therapy in four of these patients, and three patients were treated with colistin, and three were treated with tigecycline.

Assessment of Antimicrobial Therapy

The average duration of antimicrobial therapy for imipenem-cilastatin was 14.4 ± 12.5 days (291

treatment courses in 162 patients plus 18 other patients treated simultaneously with ampicillin-sulbactam and imipenem-cilastatin). Ampicillin-sulbactam duration of therapy was 13.1 ± 9.9 days and this was used in 124 treatment courses with 112 patients, of whom, 40 had ampicillin-sulbactam as initial therapy and again the 18 patients were treated with both ampicillin-sulbactam and imipenem-cilastatin. Thirty-one patients were switched from imipenem-cilastatin to ampicillin-sulbactam during treatment and 41 patients who were started on ampicillin-sulbactam were switched to imipenem-cilastatin. This most often reflected changes in attending physician and physician preference rather than a change in susceptibility. For 102 treatment courses, an antimicrobial agent other than ampicillin-sulbactam or imipenem-cilastatin was added to a total of 471 antimicrobial treatment courses used in the 281 infected patients. This was most often due to concomitant infection with another Gram-negative bacillus. For 133 survivors of 223 ventilated patients (60%) with persisting sputum cultures, median ventilator support was 28 days. (intraquartile range: 18–43 days). The mean duration of therapy with antimicrobial agents for ventilated patients were 32 days (intraquartile range: 21–45 days). For 69 of these patients, nebulization of tobramycin, amikacin, or colistin was added to the systemic antimicrobial regimen due to persistence of *A. baumannii* in respiratory tract infections. These data were reported separately.²⁵

For patients with creatinine clearances <50 ml/min, imipenem-cilastatin doses were 21.3 ± 10 mg/kg/day (range 5.5–39.7 mg/kg/day), whereas patients with creatinine clearance >50 ml/min received 52.3 ± 9.3 mg/kg/day (range 40.43–81.6 mg/kg/day). The prescribing information recommends not exceeding doses of 40 mg/kg/day. For patients treated with ampicillin-sulbactam and creatinine clearance <50 ml/min, 227 ± 10.4 mg/kg/day of ampicillin was prescribed (range 137.3–407.5 mg/kg/day). For patients with creatinine clearance >50 ml/min, 268.0 ± 105.5 mg/kg/day was prescribed (range 196.3–948.6 mg/kg/day). Doses clearly exceeded usual doses of antibiotics used in nonthermal injury patients.

Antibiotic response is outlined in Table 3 where differences in the percentage of ventilated patients, differences in percentage burn surface area involvement, and the actual and predicted survival are provided. Percentage survival reflected severity of illness in these antibiotic treatment strata and warrant caveats in extrapolating these responses to other burn centers.

As a final post hoc analysis, the response of the three most commonly used antimicrobial agents: imipenem-cilastatin, ampicillin-sulbactam, and cefepime were compared by matching three sets of 40 patients based on age and percentage TBSA burn. Assessment of any survival difference was done by χ^2 analysis ($\chi^2 = 2.236$; $P = .306$). Smoking status, ethanol use, history of hypertension, diabetes, cardiac disease, and inhalation injury were not different.

Table 3. Patients stratified by renal function ranges

Creatinine Clearance	Age	TBSA Burn	LOS	ISS	Survival Probability	Alternate Probability
<25						
Average	57.6	15.4	42.8	11.7	0.71	0.82
Standard Deviation	32.8	17.3	33.2	12.3	0.27	0.21
25.1–50						
Average	68.6	25.0	38.9	10.9	0.63	0.82
Standard Deviation	22.2	25.4	26.9	10.8	0.30	0.14
50.1–100						
Average	50.2	29.1	39.3	18.3	0.83	0.80
Standard Deviation	17.2	25.0	28.2	15.8	0.26	0.24
100.1–125						
Average	35.0	35.7	42.0	23.3	0.90	0.87
Standard Deviation	11.4	25.6	33.9	11.3	0.18	0.23
>125						
Average	30.0	28.0	35.1	17.0	0.99	0.97
Standard Deviation	9.4	22.4	24.7	10.6	0.01	0.03
F value	37.76	3.11	0.475	2.040	3.914	1.775
P value	<.05	<.05	NS	NS	<.05	NS

LOS, length of stay; ISS, Injury Severity Score; NS, not significant

ANOVA demonstrated no statistical difference in age, percentage TBSA burn, LOS, ISS score, or burn survival probability score. Day to first *A. baumannii* culture, number of positive sputum cultures at weeks, 1, 2, 3, until the end of therapy and total number of positive sputum cultures were not statistically different for the three sets of 40 matched patients. Data were incomplete and for some analyses as few as 34 of the 40 triplicates were used in rank sum tests. The median difference in pretreatment and treatment parameters were determined as were the median treatment and posttreatment difference for daily highest temperature, WBC counts, numbers of positive cultures, and LOS were analyzed using this nonparametric test. Improvement in temperature due to antibiotic therapy favored those 34 patients treated with imipenem-cilastatin (confidence intervals 20.82 and 0.28). Analysis of total sputum, central venous catheter, blood, and wound cultures for the 45 triplicates favored imipenem-cilastatin with the fewest total number of cultures (confidence interval 30.95 and 7.27). Mean arterial pressure and LOS did not differ.

For most patients, a single agent therapy was used initially with addition of other agents based on response. Response to individual antibiotics is provided in Table 4. Eradication generally was poorly accomplished with the initially chosen antibiotic with the exception of those patients given aminoglycosides. Consistent with other reports, persistence of *A. baumannii* was common and duration of antibiotic therapy was more than 21 days in 40% of the treated patients. Treatment failure with the initial antibiotic regimen selected occurred in one-in-six to one-in-four patients.

Table 4. Differences in eradication, persistence, and treatment failure for patients with *Acinetobacter baumannii* treated with antibiotics

	N	Eradicated (%)	Persisted (%)	Failure (%)
All patients	281	28	54	18
Imipenem-cilastatin	162	26	57	17
Ampicillin-sulbactam	40	18	57	25
Imipenem-cilastatin + Ampicillin-sulbactam	18	44	31	25
Cefepime/ceftazidime	41	31	56	13
Ciprofloxacin/ levofloxacin	9	40	50	10
Colistin	3	17	83	0
Tigecycline	3	50	33	17
Amikacin/tobramycin	4	100	0	0

DISCUSSION

A. baumannii has been steadily emerging as a polyresistant organism in intensive care.^{2,3,5,6} Problems with *A. baumannii* can be attributed to the progressive development of multiple resistance genes.^{17,18,26} *Acinetobacter* species possess multiple beta lactamases capable of inactivating cephalosporins, penicillins, monobactams, and even carbapenems.^{5,16,27} *Acinetobacter* species also possess approximately two to three separate "efflux pumps"^{9,10} that actively remove antimicrobial agents. Our *A. baumannii* isolates routinely demonstrated MDR susceptibility patterns in more than 80% of our isolates. Most commonly, the *A. baumannii* susceptibility demonstrated resistance to all antimicrobial agents with a MIC of >8 mg/L for imipenem-cilastatin, >8/32 for ampicillin-sulbactam, and >16 for amikacin. A variant clone was also isolated which demonstrated intermediate susceptibility to one or more of the antimicrobial agents above. In response to these susceptibility patterns and known differences in pharmacokinetics in burn patients, aggressive antimicrobial agent regimens were used such as imipenem-cilastatin at ≥ 40 mg/kg/day, ampicillin-sulbactam at 6 g doses every 6 hours, and high doses of cephalosporins at 2 g every 8 hours.

Acinetobacter species is capable of expressing or suppressing its antimicrobial resistance genes confusing antimicrobial agent susceptibility determination.^{18,28} Repeated susceptibility testing in our laboratory and at the laboratory assessing the genetic difference in our isolates demonstrated that different resistance genes were occasionally expressed that differed from the initial in vitro testing. Media used in semiautomated susceptibility testing equipment delayed susceptibility reporting.²⁹

Our decision to treat apparent *A. baumannii* infection was also complicated by an unclear separation between colonized patients and infected thermal injury patients.^{5,24} For several colonized patients short courses of imipenem-cilastatin or ampicillin-sulbactam were initiated; however, duration of therapy was <4 days. As an interim analysis of our data in 2005, we looked at 157 *A. baumannii* nosocomial pneumonias in ventilated and nonventilated patients, the response to ampicillin-sulbactam at doses providing 2 g of sulbactam. When compared to imipenem-cilastatin 0.75 to 1 g every 6 hours, imipenem-cilastatin appeared to resolve infections more quickly.^{19,20} Response to any antimicrobial therapy though was slower than expected for ventilator-associated pneumonia based on the American Thoracic Society VAP Guidelines.³⁰

Antimicrobial use in thermal injury has been described extensively for the aminoglycoside class of antibiotics.^{31,32} In addition, pharmacokinetic studies using cefepime, ciprofloxacin, and other antimicrobial agents³³ have demonstrated a larger required dose.

The average percentage burn for these *A. baumannii* infected patients was 30% indicating that *A. baumannii* infection was most often associated with large burns. This study was limited by retrospective analysis of patient parameters thus we were only able to make some assessment of the antimicrobial agents used. Persistence in positive cultures indicated that the doses chosen for treatment of infected patients, though quite aggressive, still resulted in a slow response. On average, 14 positive cultures per antimicrobial agent treated patient and indicating approximately three weeks of therapy on average based on three cultures per week routine culture. For the 45 patients with only wound infections, the least ill group in the analysis (based on average TBSA percentage), 19 (40%) also had persisting wound cultures for more than 21 days. For the 133 patients of the 223 ventilator-dependent patients, median duration of support was 28 days. Only four survivors were treated for less than eight days of antimicrobial therapy. An additional nine patients required less than 14 days of therapy (7%) and only 29 of the 133 (22%) met the goal of treatment for less than 21 days of antimicrobial therapy according to the American Thoracic Society guidelines. For 101 of the 133 patients with pneumonia (76%), therapy exceeded 21 days and for 34 of these patients antimicrobial therapy exceeded 45 days (25%).

For *A. baumannii*, response following treatment with amikacin, imipenem-cilastatin, a third-generation cephalosporin, and ampicillin-sulbactam as single agents or in combination no demonstrable superiority has been noted and our experience confirms other reports.^{3,23,24,34} Imipenem-cilastatin was the most effective therapy; however, organism persistence and nosocomial spread indicate that total eradication of *A. baumannii* with any antibiotic therapy is a problem.³⁵

Colistin and a new agent, tigecycline, have limited published studies demonstrating efficacy in *A. baumannii* infections.³⁶ Our limited use of tigecycline, and colistin does not provide any additional insight concerning the efficacy of these agents against *A. baumannii*. Renal impairment correlated with infected patient nonsurvival. Renal impairment did not differ among the antimicrobial agent groups analyzed ($F = 1.474$; $P > .05$) and did not explain any difference in survival.

Assessment of the currently used therapies did not provide insight on empiric treatment of *A. baumannii* infections. The interim analysis of *A. baumannii* pneumonia patients had suggested that imipenem-cilastatin was the most effective therapy but this did not represent a "head-to-head" comparison of the agents. A planned prospective study imipenem-cilastatin versus tigecycline and colistin was never initiated. Elimination of the two clones of *A. baumannii* eliminated further evaluation of antimicrobial agents against these clones.

As a final post hoc analysis, the 40 patients treated with ampicillin-sulbactam were compared to 40 imipenem-cilastatin and 40 cephalosporin patients with approximately the same age and TBSA%. Complete data were available for 34 patients in each group. ANOVA demonstrated no difference in age or percentage of burn. In addition, no differences in start of treatment, WBC count, serum creatinine, creatinine clearance, LOS, ISS score, burn survival score, or day postadmission isolation of *A. baumannii* was demonstrable. The number of positive sputum cultures did not differ for the 40 patient triplicates. The median difference in parameters for the three treatment groups were analyzed using the Kruskal-Wallis test. With equal numbers of patients in each group, this nonparametric statistical test favored imipenem-cilastatin therapy. LOS, probably more clinically significant, did not differ among the three groups and was a disappointing finding.

Our goal was to determine the most effective agent for empiric treatment of our MDR *A. baumannii* as part of the Multidisciplinary Performance Improvement Burn Center Task Force. As is noted in Table 4, treatment response was less than optimal and from the data above, duration of antibiotic therapy indicates "sluggish" response to antimicrobial therapy. The most effective therapy was to contain the MDRO *A. baumannii* and to use at that time aggressive antimicrobial therapy to reduce the bioburden of the patients and appropriate cleaning to reduce the bioburden of the unit.

In conclusion, *A. baumannii* is a persisting organism that it difficult to eradicate. Rigorous infection control practices halted cross contamination and aggressive cleaning, high doses of antimicrobial agents, and strict infection control enabled us to ultimately eradicate the MDR *A. baumannii*; however, the doses used resulted in persistence in more than half of treated patients.

The most obvious limitation of this study was the retrospective data collection. As the first part of a planned study to investigate the response of antibiotics to a MDRO *A. baumannii* and its related

clone it suffered from many methodologic flaws associated with retrospective analysis. The interim analysis provided insight to the organism and its behavior as did the testing of the 100 samples for clonality and susceptibility at an independent facility. Specifically for our two clones ampicillin-sulbactam demonstrated slower responses to 6 g of ampicillin-sulbactam than to 1 g every 6 hours of imipenem-cilastatin. These response differences may reflect our two clones exclusively. Given that *A. baumannii* is a mixture of several variants, this is not surprising that some investigators will find marked differences in antibiotic response among published studies. The response of imipenem-cilastatin when compared to other agents used in treatment of infections with these two clones naturally changed physician practice in favor of the perceived better antibiotic regimen. As a retrospective review, this could not be controlled. Presentation of interim analysis in 2005 may also have influenced antibiotic prescribing. The eradication of our “study organism” probably had the most effect on this study in that it prevented us from a true “head-to-head” prospective comparison of three of the antibiotics we were using.

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Abstract

INTRODUCTION: Over a 15 year period, our burn treatment center noted a pattern of AB resistance suspicious for a specific resistance clone and its variant. AB resistance was addressed via development of a multidisciplinary team to investigate and propose solutions to this problem.

METHODS: An outside hospital epidemiologist consultant assessed infection control practices at an on-site visit of the burn treatment center and the intensive care units. The following recommendations were made: 1) establish AB control goals, 2) collect data on antibiotic use and AB isolation, 3) continue surveillance cultures, 4) redesign of the burn treatment center, and 5) redesign the hydrotherapy area. Immediate changes included: 1) contact isolation procedures according to the Centers for Disease Control, 2) cohorting AB patients, 3) individualization of all patient care equipment, 4) evaluation of cleaning solutions in use, and 5) if necessary total unit terminal cleaning.

RESULTS: Comparison of multi-year cycles demonstrated a random process of "high" and "low" AB isolation (See graph below). The low yield of environmental and health care workers hand cultures did not correlate with AB recovery from patient cultures. Routine surveillance cultures of patient care areas sought out a potential nidus of AB. Surveillance cultures recovered multi resistant organisms with rare isolation of AB. Modification of behaviors and revision of cleaning practices improved environmental culture results.

CONCLUSION: Initiation of stringent hand washing and adherence to infection control guidelines eliminated both clones of AB. Chlorhexidine for handwashing is impaired by organic contaminants and may explain the low level persistence of AB in properly washed hands. Our successful approach and progressive control of the organism did not require closing of the burn unit. Although we never found the "one" source, we did identify and eliminate the sites that revealed positive cultures and modified likely processes that promoted contamination. Ultimately we were successful in eliminating our resistant AB clones.

INTRODUCTION

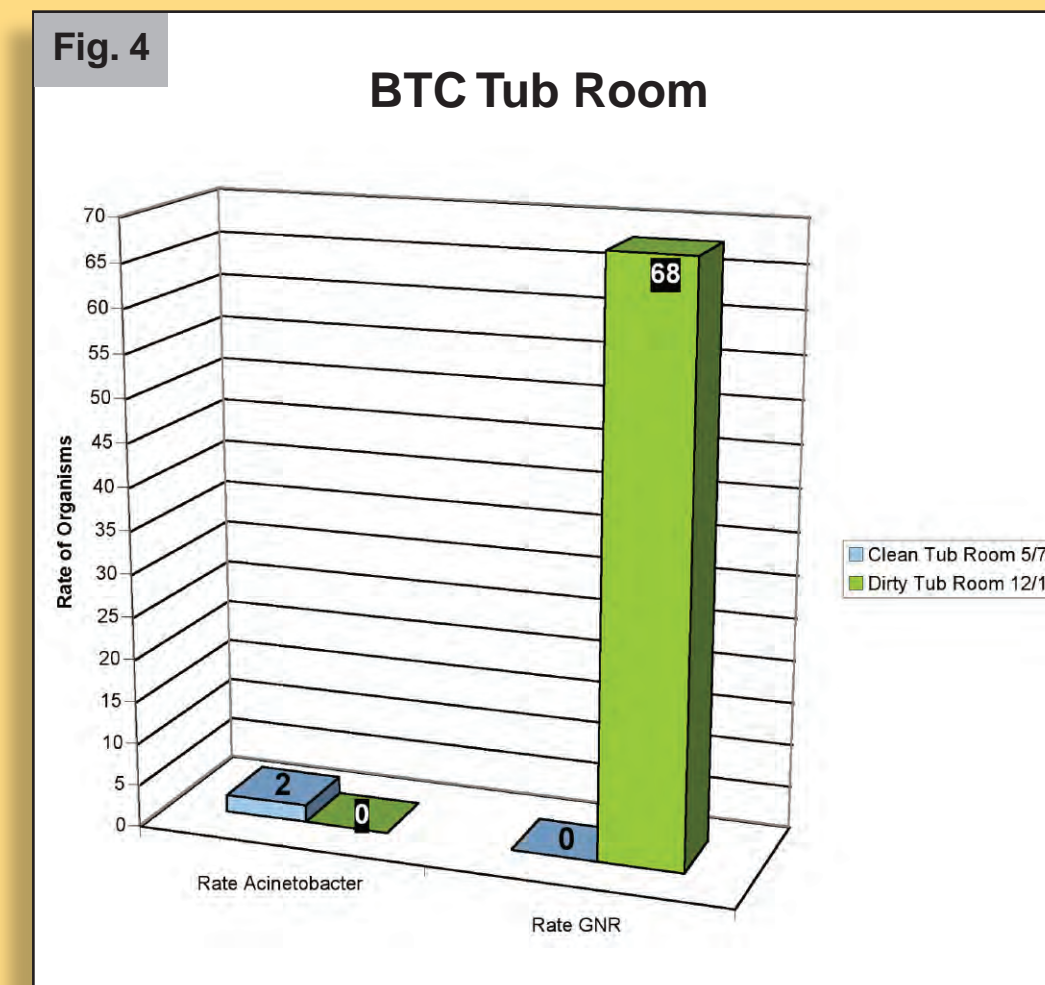
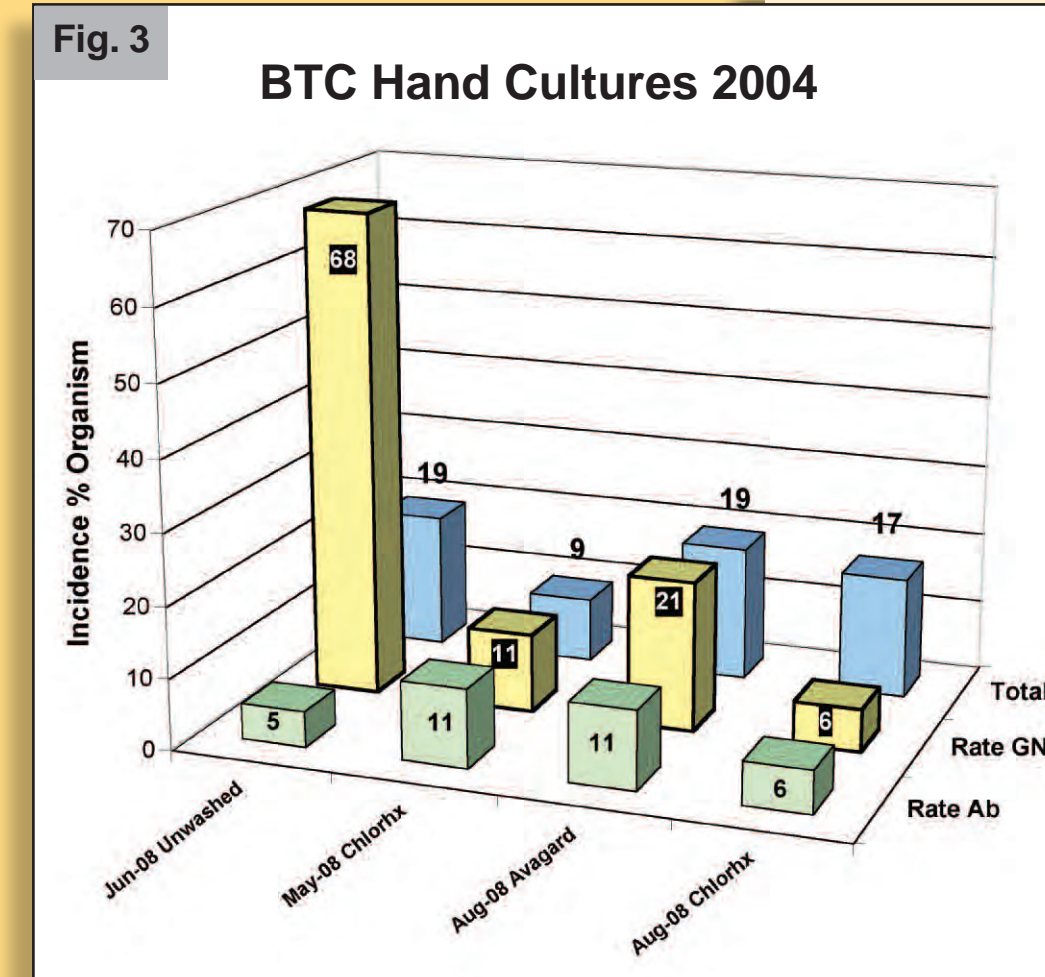
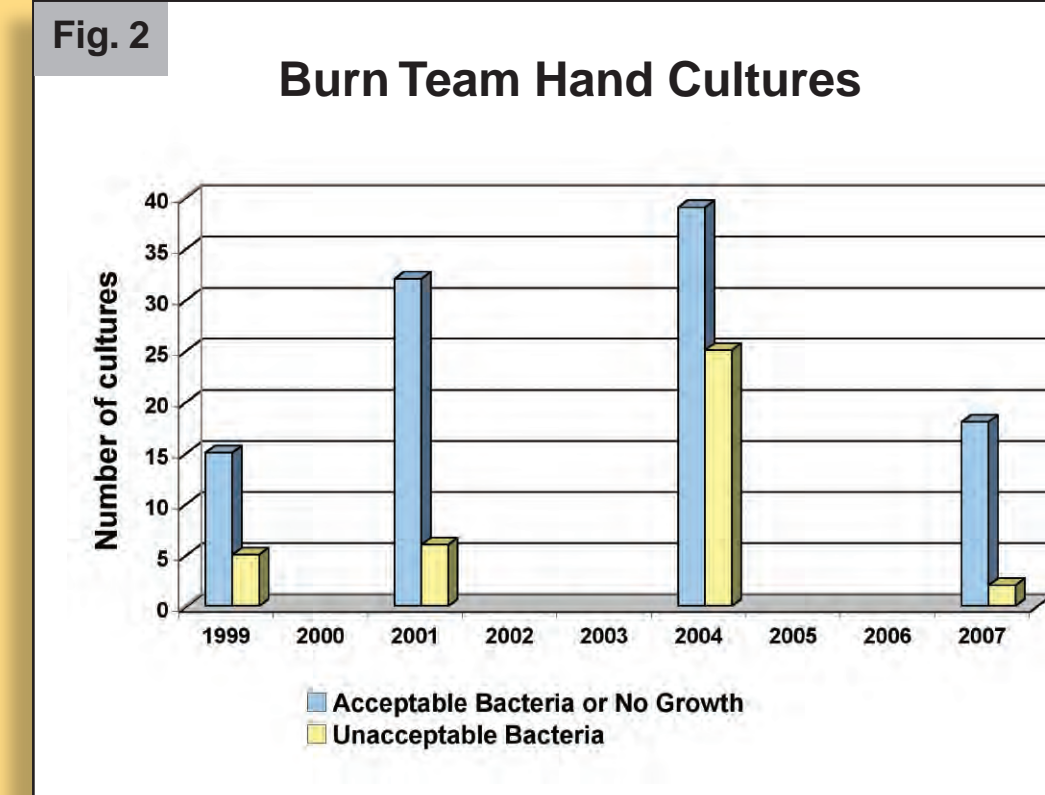
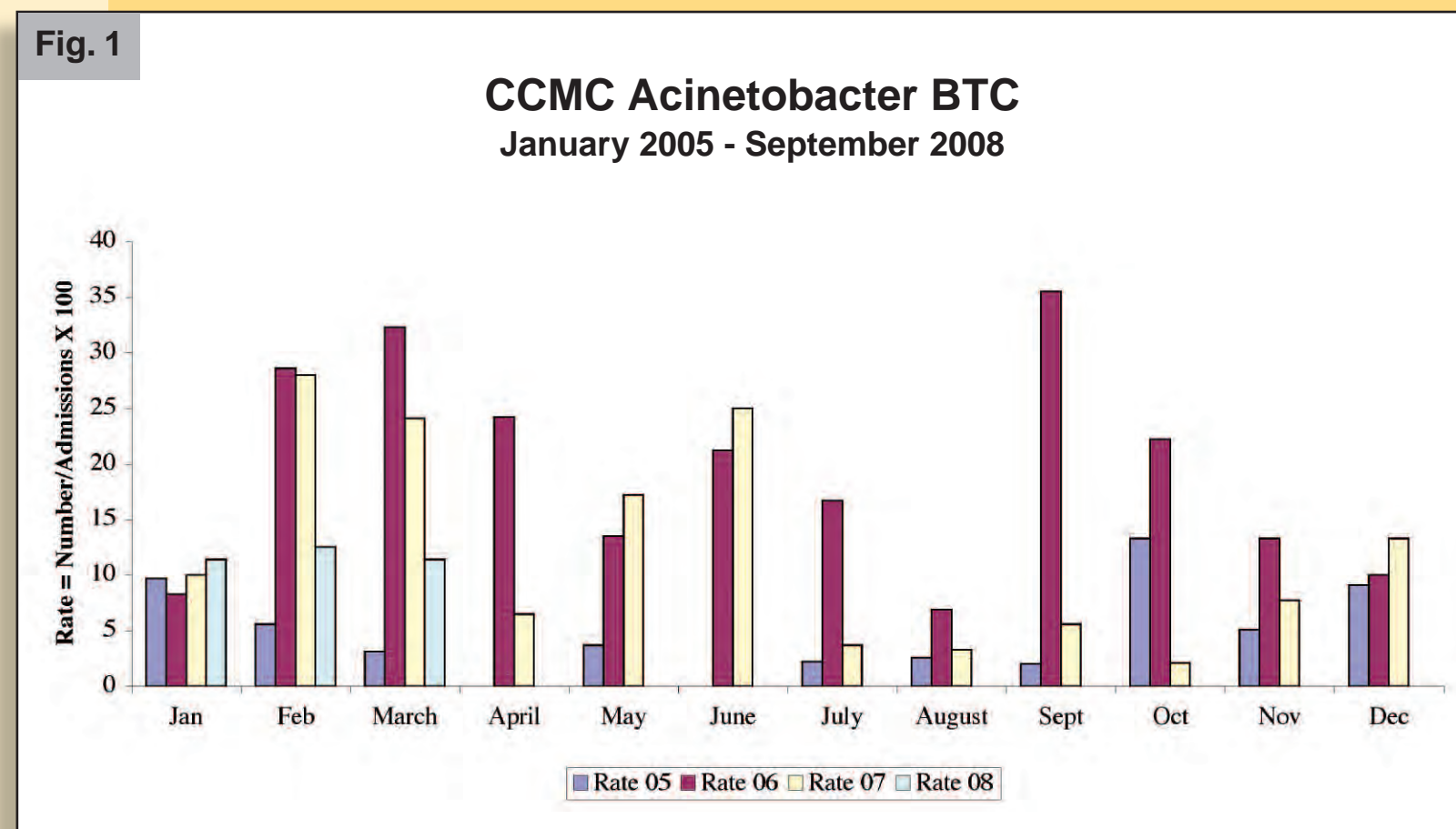
Acinetobacter baumannii (AB) is a poly-resistant organism resident in burn treatment centers. Though isolation of AB, increased from 2000-2003, no source was determined by environmental cultures. The warm, wet environment of the hydrotherapy area is ideal for this organism; however it can survive for one year in arid and inhospitable environments. The infectious disease section chair called together A Multidisciplinary Performance Improvement Task Force to explore a means for permanent eradication. Extensive literature review on outbreaks of AB and its spread have been reported and were also reviewed. Room cleaning, patient isolation, hand washing protocols were reviewed along with more aggressive surveillance culturing. These findings directed changes in the environment and patient care practices that sustained elimination of AB. Use of Resuscitation fluids, colloids, the extent of burn injury, transfusions, and agents used in stress ulcer prophylaxis were evaluated. The physical layout was also reviewed with a goal of improving infection control. Routine hand washing with hand cleansers containing chlorhexidine demonstrated persistence of AB on post-hand washing cultures. Multiple institutions have demonstrated persistence of AB on health care professional lab coats, scrubs, and privacy curtains indicating that standard cleaning methods allowed AB a niche in our burn treatment center.

METHODS

Our regional burn center serves a four state area that includes parts of Pennsylvania, New Jersey, Maryland and the entire state of Delaware. The burn center consists of 10 private rooms and 2 semi-private rooms capable of supporting all levels of care and it admits greater than 475 pediatric and adult patients annually following admission ABA criteria. A hospital epidemiologist consultant assessed our practices following an on-site review and made the following recommendations: 1) establish organism control goals, 2) assess antibiotic use and isolation of AB in the hospital, 3) continue surveillance cultures, 4) redesign unit for individual patient care areas, and 5) redesign the hydrotherapy area. Infection control practice changes included: 1) CDC contact isolation procedures, 2) cohorting of AB patients, 3) use of disposable equipment, 4) evaluate cleaning solutions, and 5) if necessary close the unit for total unit terminal cleaning.

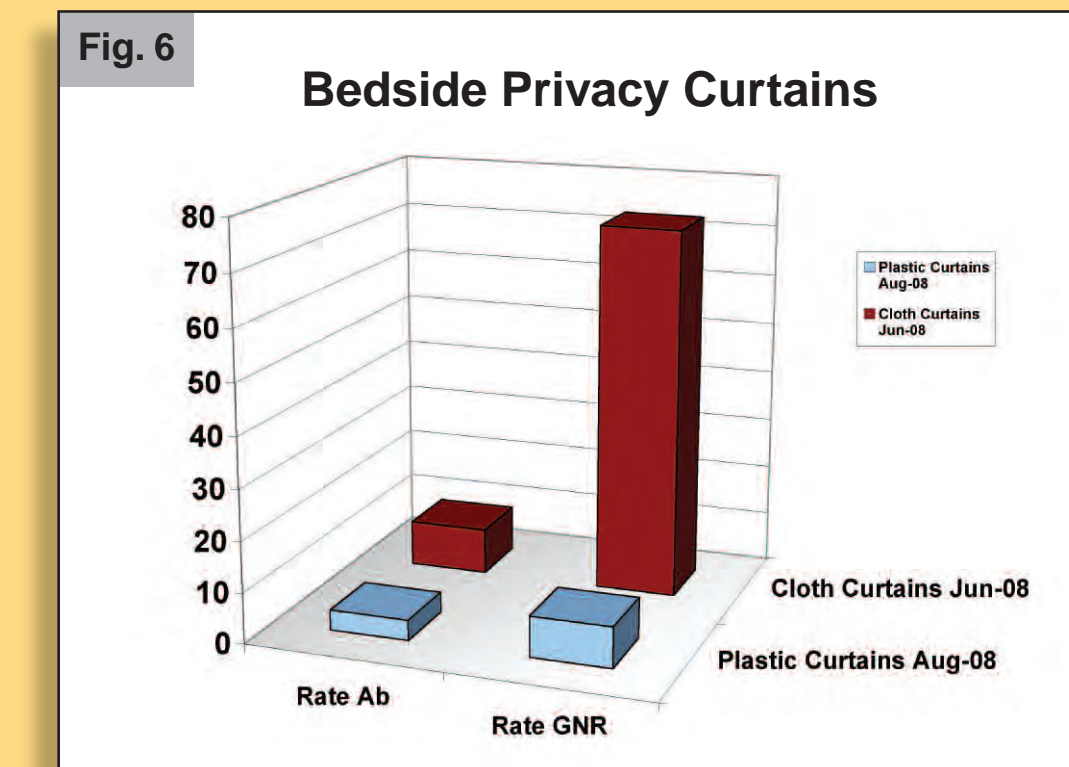
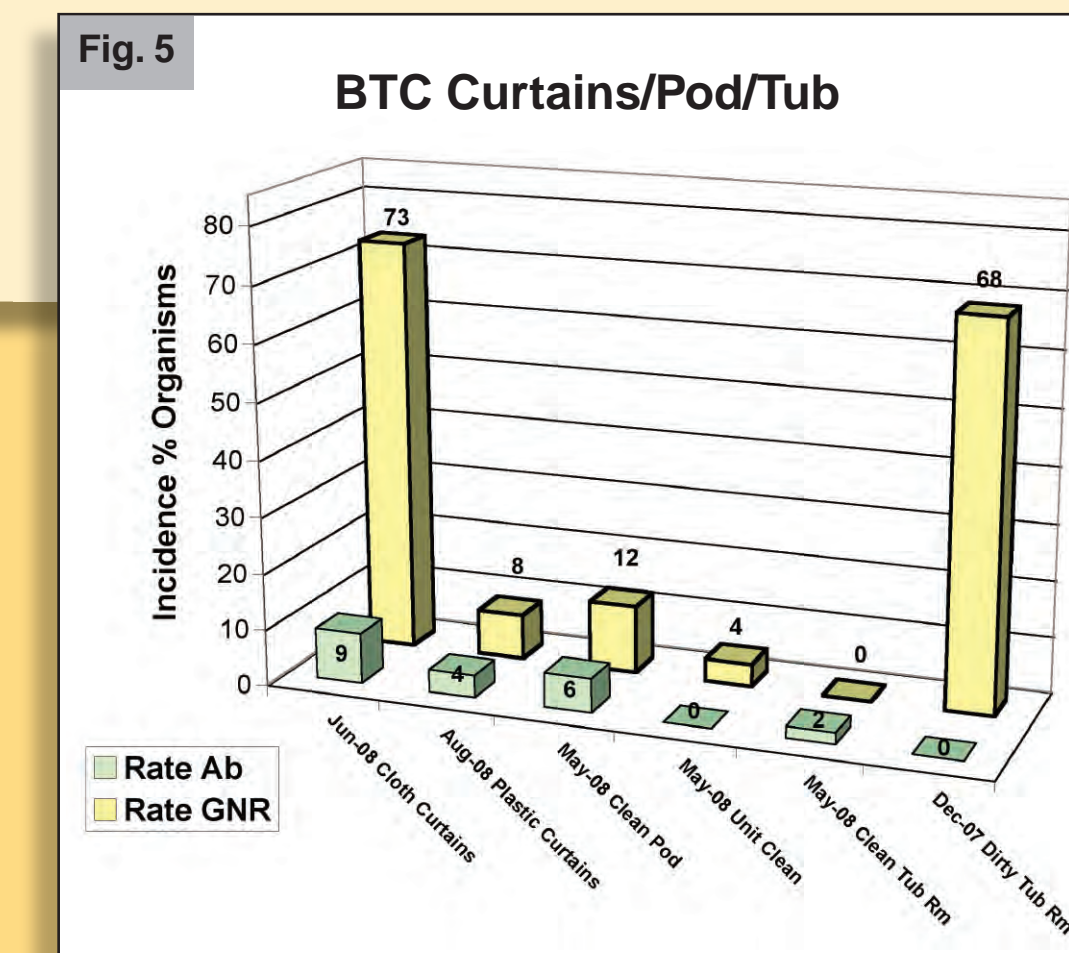
Random cultures were reviewed from 2000 to 2003 from patient care areas. AB was isolated from keyboards, telephones, and light switches. A specific antibiotic use protocol was developed based on experience and review of the literature. The patient care processes were also critically reviewed. Environmental cultures noted acceptable and unacceptable bacterial organism isolation from the environment. Isolation of organisms from hand cultures from 1999 to 2007 were reviewed. Cultures obtained following reinforcement of infection control policies documented a steady decline in Gram-neg bacteria isolation from the hands; however, persistence of AB was noted.

Procedural cleaning by EVS needed to be addressed and literature review of epidemiologic spread of AB guided further approaches to the persistence of AB. Infection control patient care protocol compliance was monitored. Comparison of multi-year cycles failed to demonstrate "problem months." Selected AB isolates were sent for extensive susceptibility and genetic testing indicating a single AB clone and its variant.



RESULTS

Hand cultures were obtained from 1999-2007 demonstrated unacceptable Gram-neg and Gram-pos pathogenic organisms and low-level recovery of AB. (See FIG 2). An observed timed handwashing technique comparing chlorhexidine and a waterless alcohol lotion product. (See FIG 3) Hand washing failed to consistently eradicate Gram-negative organisms indicating that standard infection control procedures would not eliminate the risk of sporadic spread of AB. The low yield of environmental and health care workers hand cultures was in contrast to the high incidence of AB in patient cultures. Specific patient care areas recovered AB during renovation of the tub room, patient shower area, and dressing change rooms. (See FIGS 4 and 5) Scrubs and the fabric curtains were contaminated with AB (See FIG 6) warranting redesign of apron coverings used in patient care areas. Renovation was focused on ease of cleaning, better work flow, limiting contamination. Modification of health care workers behaviors, including review and revision of cleaning practices, was demonstrated by improved hand and environmental culture results.



CONCLUSIONS

In 2004, disposable aprons cover which was consistently used by professionals prior to entering patient care areas. Other equipment were provided and used. Plastic curtains were ordered and used. Plastic curtains were installed on the clean side of the tub room.

The patient care areas noted as potentially contaminated areas in color of the floor tile. Individual hand washing compliance with hand dispensers. Cloth curtains were replaced with plastic curtains. Plastic curtains counts and in collaboration with the plastic disposable privacy curtains (See FIGURE 6) The plastic curtains hanging process eliminating the cloth curtain. The clean curtain is hung in a way that the new curtain is clean.

In 2008, the installation of glass pod into individual rooms. Plastic desks were installed with a cross contamination during cleaning.

Surveillance cultures revealed cleaned by environmental services. Cleaning of common patient monitors and electrical equipment by professionals. Sodium hypochlorite selective cleaning of hard surfaces.



Abstract

INTRODUCTION: *Acinetobacter baumannii* is a non-fermentive Gram-negative cocci-bacillus with multiple resistance genes isolated with increasing frequency in intensive care units.

METHODS: Electronic microbiology records were inquired for thermal injury patients with isolation of *A. baumannii* (AB) from sputum, blood, or wound cultures. Patients were designated as “colonized” (COL) if a single AB culture was obtained and considered “infected” (INF) if AB isolates were obtained from 2 or more sites or at 2 or more time periods. INF patients were then evaluated for whether or not they had been treated with antibiotics for which the isolate was sensitive.

RESULTS: Isolates (N = 8729) from INF (N = 308) demonstrated susceptibility to ciprofloxacin, cefepime, imipenem cilistatin (IC), ampicillin sulbactam (AS), colistin, and tigecycline. Chi-square analysis as “eradicated,” “persisting,” and “failure” for these six antimicrobial agents did not differ ($X^2 = 5.2873$; $p \gg 0.05$). T-test comparison of the 45 COL versus 308 INF demonstrated no difference in age, height, weight, or initial laboratory tests. Day to first *A. baumannii* culture also did not differ between COL and INF. As expected, total body surface area burn (T = 4.28256; $p \ll 0.05$) and length of stay (T = 4.0475; $p \ll 0.05$) were greater in INF. All 45 COL survived; however only 207 INF survived (76.9%). T-test analysis of INF survival status noted that non-survivors were older (T = 2.1207; $P = 0.03$), had larger burns (T = 3.1157; $p \ll 0.05$), had lower serum albumin levels (T = 2.0214; $p = 0.04$), and had positive cultures sooner (T = 2.9108; $p \ll 0.05$). For INF, inhalation injury did not predict increased mortality ($X^2 = 0.5535$; $p \gg 0.05$). Stratification by mg/kg dose and renal function of IC and AS demonstrated no difference in eradication, persistence, or failure for doses < 40 mg/kg and < 250 mg/kg and for doses > 40 mg/kg and > 250 mg/kg for IC ($X^2 = 2.47$; $P \gg 0.5$) and AS ($X^2 = 4.39$; $P \gg 0.05$), respectively. Difference in time to eradication and a few other parameters remain to be assessed.

CONCLUSION: These initial data indicate that the chosen antibiotic and dose had no impact on AB eradication. For these multi-resistant AB INF patients nearly 25% succumbed to infection. Early isolation of AB was associated with increased risk of mortality, as was larger burns, older age, and lower albumin. AB in thermal injury patients was a persisting opportunistic INF with low virulence and high antimicrobial agent resistance for which patients “died with,” rather than “died of” AB.

INTRODUCTION

Acinetobacter baumannii (AB) is a poly-resistant organism resident in burn treatment centers. The role of antibiotic therapy on the selection and perpetuation of two resistant clones of *A. baumannii* in our unit was studied as use of antimicrobial agents was based on small studies. Distinguishing “colonization” from “infection,” confuses the decision for antibiotic therapy and susceptibility testing provided poor direction.

MATERIALS AND METHODS

All known isolates of AB from the Burn Treatment Center from 1992 to 1996 and 1999 to March 2009 were assessed (see figure 1) to distinguish colonization from infection. Demographic data are provided in Table 1.

Colonization – Patients were deemed colonized if only a single AB isolate had been isolated or no antibiotic therapy directed against the organism was prescribed.

Patients – Demographics, vital signs, laboratory values, numbers and sites of isolation, the percent total body surface area burn, past medical history, smoking and ethanol exposure, GI prophylaxis, days to first culture, doses of antimicrobials, addition or subtraction of antimicrobials, and changes in renal function were assessed for all patients.

Survival was defined as discharge alive from the BTC.

Treatment success was defined as either eradication of the organism or asymptomatic persistence

Treatment failure was defined as death or symptomatic persistence of AB cultures warranting a change in antibiotic therapy

Statistical analysis – Categorical data were analyzed with X^2 , continuous data were analyzed using student’s t-test or analysis of variance. Skewed data were log-transformed for analysis.

Table 1. Demographics

	AGE	Weight	BSA	%BURN	LOS
38 COLONIZED PATIENTS					
MEAN	42.4	82.4	1.96	17.8	25.7
STD DEV	±20.4	±24.9	±0.37	±21.7	±22.4
326 INFECTED PATIENTS					
MEAN	48.3	82.4	1.95	30.6	41.1
STD DEV	±20.6	±25.5	±0.34	±24.9	±29.6
T-test	NS	NS	NS	<<0.05	<<0.05
278 INFECTED PATIENTS WITH RECORDS					
MEAN	48.4	82.9	1.96	30.8	40.4
STD DEV	±20.7	±25.6	±0.34	±25.3	±27.7

RESULTS

4631 positive AB cultures from 364 patients were reviewed for inclusion in this IRB approved retrospective study. Males constituted 228 patients (62.6%). The figure to the lower right provides information on selection and disposition of evaluated patients. Patient data demonstrated that 184 patients were initially infected/ colonized in 184 of the 364 patients with 180 patients having later onset of isolation. Assessment by year failed to demonstrate any secular change in those presenting within 24 hours with AB from those with later infection. Inhalation injury, gender, use of acid suppression, smoking history and survival status did not differ by X^2 analysis. Figure 2 provides the breakdown of sputum cultures (scx), blood and catheter cultures (bcx) and wound cultures (wcx). Three positive urine cultures were counted with the bcx.

For the 38 patients with a single culture isolated, 5 were SCX, 3 were BCX, 30 were WCX, with wound culture predominance. All colonized patients survived their burn injury. Figure 2 shows the most frequent isolates occurred in the first 7 days for all three culture designations with large numbers occurring after the 21 day cut off. For these 326 patients 247 required ventilatory support and 231 had inhalation injury. Only 255 patients were discharged alive (78.2%). Table 2 stratifies survivors by renal function. Ranges in age, weight, and TBSA differed to a greater degree than length of stay (LOS).

Infected survivors had 3628 AB cultures with 36 to 40% obtained after more than 21 days of antibiotic therapy. For these 220 pts, persistence in days was 21.8 ± 16.6 days. For ten of these pts a second infection with this organism occurred with persistence for 21.0 ± 13.6 days. For a single pt two other episodes of 22 days and 27 days occurred before discharge. For the 208 survivors with data, 35 pts were not treated with either ampicillin sulbactam (AS) or imipenem cilistatin (IC). IC was used in 149 pts (191 treatment courses) and AS in 71 pts (86 treatment courses) with considerable overlap between groups. The mean duration of IC therapy was 16.2 ± 15 days and for AS 13.2 ± 9.8 days with considerable skew and kurtosis for both. Log transformation normalized distributions with a mean \pm standard deviation of 11.0 ± 2.4 days and 10.0 ± 2 days for IC and AS, respectively. Cefepime was used in 29 of the 35 pts (mean treatment duration 12.7 ± 5.9 days) often in combination with ciprofloxacin (16 pts, 9.5 ± 5.4 days) or moxifloxacin (4 pts) levofloxacin (1 pt). Tigecycline was used in 3 pts (duration 10.3 ± 2.1 days) and colistimethate in 6 pts (duration 12.8 ± 6.9 days) indicating that choice of antibiotic had little impact on duration of treatment / eradication of the organism. Minimum inhibitory concentrations (MIC) were determined by a semi-automated system showed MICs of >8 mg/L, >16mg/L, and >8 mg/L for imipenem, amikacin, and ampicillin sulbactam respectively. Susceptibility to colistin and tigecycline were also determined with initial susceptibility.

For 30 pts with incomplete data but complete antibiotic data, IC duration was 15.9 ± 10.2 days (transformed: 12.2 ± 2.2 days) and AS was 12.2 ± 10.9 (transformed: 8.2 ± 2.4 days). These data inferred for our patient population that doses of 6 g every 6 hours of AS and 1g every 6 hours of IC did not differ substantially eradication of AB from survivors.

Breakdown of Reviewed Charts

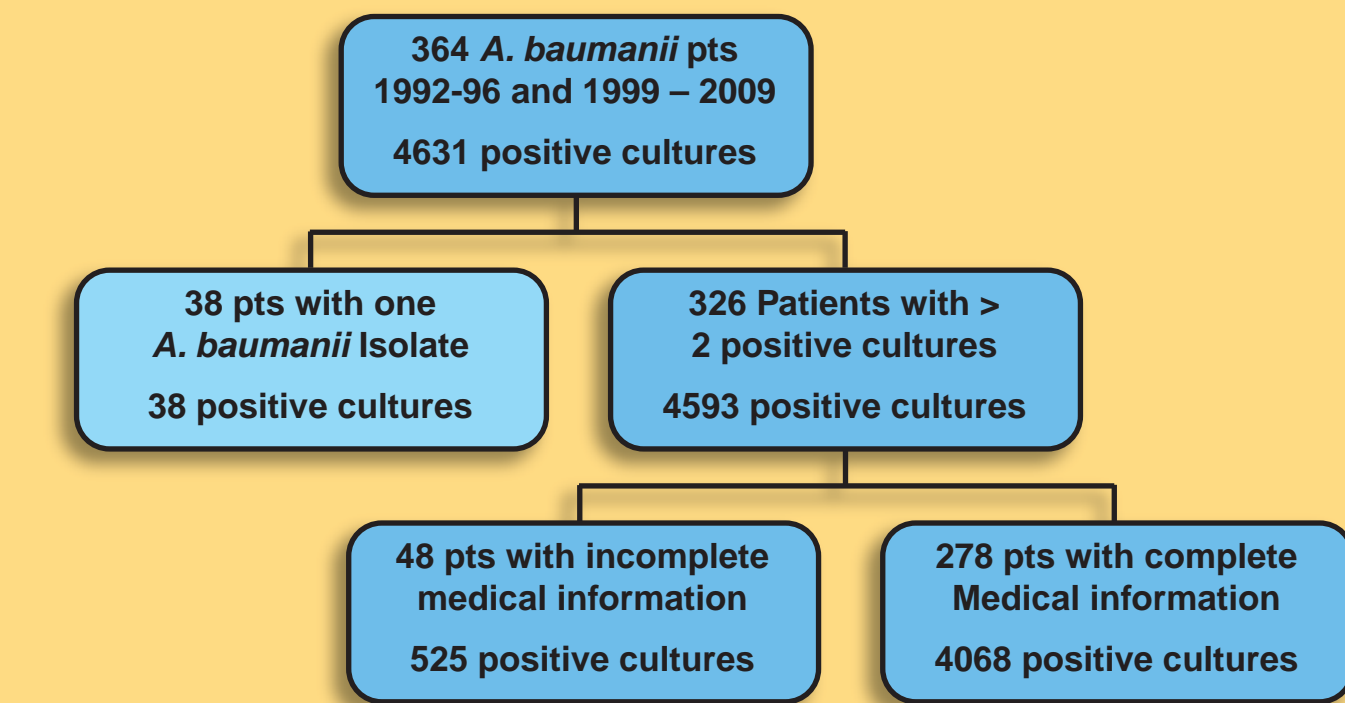


Table 2. Stratified Renal Function of Survivors

	Sex	Age	Wt	TBSA	LOS
Creatinine Clearance < 25 mL/min					
MEAN	M = 5	52.6	63.9	15.7	50
STD DEV	F = 5	± 36.7	± 38.3	± 21	± 29
Creatinine Clearance 25 - 50 mL/min					
MEAN	M = 9	67.9	67.6	24.7	45.9
STD DEV	F = 17	± 23	± 17.9	± 24.3	± 31.5
Creatine Clearance 51-100 mL/min					
MEAN	M = 77	50.1	75.9	28	46.5
STD DEV	F=58	± 18.1	± 18.8	± 23.2	± 28.9
Creatinine Clearance 101-125 mL/min					
MEAN	M = 51	34.8	92.1	30.4	42.5
STD DEV	F = 8	± 12.2	± 21.5	± 22.4	± 34.7
Creatinine Clearance > 125 mL/min					
MEAN	M = 22	31.3	122.4	28.4	40.2
STD DEV	F = 3	± 3.8	± 27.2	± 18.5	± 26.1

CONCLUSION

The optimal use of AB is desirable in a burn patient. Selection of the optimal dose of resistant AB is a balance of resistant AB colonization/ infection, requiring monias, requiring Selection of the optimal dose of resistant AB is a balance of resistant AB colonization/ infection, requiring monias, requiring Selection of the optimal dose of resistant AB is a balance of resistant AB colonization/ infection, requiring monias, requiring

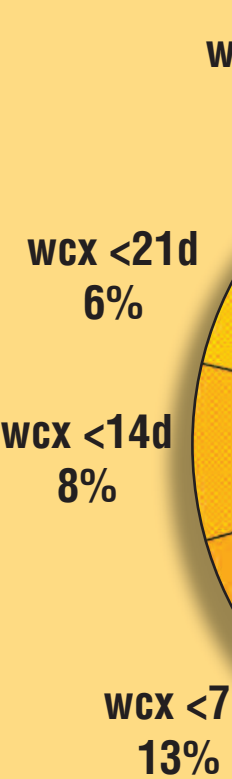
Selection of the optimal dose of resistant AB is a balance of resistant AB colonization/ infection, requiring monias, requiring Selection of the optimal dose of resistant AB is a balance of resistant AB colonization/ infection, requiring monias, requiring

Aggressive doses of AB are similar LOS in patients with <50 mL/min velocity.

The eradication of the AB is interdependent on the doses of AB, IC, and AS.

Infection control in burn treatment centers is of AB.

A. baumannii blood or



Amlodipine-Induced Toxic Epidermal Necrolysis

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The objective of this study is to report a case of amlodipine-induced dermatotoxicity following treatment for diabetic nephropathy. Although other members of the dihydropyridine calcium channel blockers have been reported to cause dermatotoxic reactions, this is the first report attributing this effect to amlodipine. A 71-year-old diabetic and hypertensive woman had been noted to have worsened renal dysfunction and hyperkalemia attributed to enalapril, thus a trial of amlodipine was begun. On day 12 of amlodipine therapy, the patient developed a pruritic maculopapular rash on her hands for which she sought medical attention. On day 16, she presented again to the emergency department now with hives and small blisters involving the trunk and arms with ~25% TBSA involvement warranting transfer to a regional burn treatment center. The rash progressed after admission to 48.5% TBSA and included conjunctival sloughing. The patient's hospital course was uneventful, and she was discharged after 8 days. Drug-induced dermatotoxicity presenting as toxic epidermal necrolysis is often caused by antibiotics and anti-epileptic medications; however, calcium channel blockers are an uncommon cause. The Naranjo assessment yielded a score of 5, and the SCORTEN was 4 with a predicted mortality of 58%. This report represents the first published case of amlodipine-induced toxic epidermal necrolysis. (*J Burn Care Res* 2011;32:e158–e160)

Drug-induced dermatotoxicity presents as Stevens Johnson Syndrome (SJS) if there is <10% TBSA, SJS toxic epidermal necrolysis (SJS-TENS) overlap if TBSA is between 10 and 30%, and TENS if >30% TBSA is involved.^{1–5} SJS and TENS result from generation of nitrous oxide, release of soluble FAS ligand (FASL), interaction of FASL with FAS (the keratinocyte apoptosis receptor or CD95) on epidermal tissue, and action on exposed drug-tissue complexes.^{2,5–7} Plasma levels of soluble FASL are elevated in the initial phase of the reaction but drop off rapidly as the maculopapular rash progresses. The acute phase begins during the first 4 to 12 days of drug exposure with an acute macular rash followed by coalescence of macules and desquamation. Activation of lymphocytes, release of inflammatory mediators, release of cytokines and pep-

tides, and antibody production cause blistering, exfoliation, and confluence of the rash.⁸

Cutaneous drug-induced reactions have been associated with sulfonamides, antiepileptic medications, nonsteroidal anti-inflammatory drugs, and other medications.⁴ Prompt discontinuation of all suspected medications represent the most important step in the initial management of a drug-induced rash. Because of water loss and infection risk from these wounds, it is recommended that the patient be transferred to a burn treatment center or facility with expertise in management of large open wounds.^{2,7,9}

The choice of a calcium channel blocker as an alternative to an angiotensin-converting enzyme inhibitors was appropriate for this patient with diabetic nephropathy and hypertensive renal disease. Severe rash has been reported for all of the calcium channel blockers; however, diltiazem has been reported most frequently.¹⁰ Nifedipine and verapamil have been implicated in causing both SJS and TENS.^{10–13}

CASE REPORT

A 71-year-old diabetic woman with polycystic kidney disease and hypertension, was initiated on amlodipine

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after enalapril had demonstrated worsening of renal function, proteinuria, and hyperkalemia. Thus, a change from enalapril to 5 mg of amlodipine was suggested with continuation of medications for management of hyperlipidemia and hypertension. Twelve days after starting amlodipine therapy, the patient developed a pruritic maculopapular rash involving both hands, warranting an appointment with her primary care provider. Given the rapid onset of rash, amlodipine was discontinued and the patient was restarted on her previous enalapril dose. On day 14 of exposure, she sought emergency department care because of further extension of the rash from her arms to her chest now presenting as "weeping hives" with minimal blistering. Medical management of the rash was limited to a methylprednisolone scheduled taper product (Medrol dose pak®) and diphenhydramine. On day 18 postexposure, the rash had progressed further and was described as a confluent maculopapular rash which warranted a second visit to the emergency department. On examination, the rash now was described as "reddened" hives involving the trunk and arms with small (approximately 5–10 mm) blisters now involving the oral mucosa, although blistering areas remained Nikolsky sign negative. Laboratory findings before transfer were unremarkable with the exception of blood urea nitrogen of 99 and serum creatinine of 3.7 mg/dl. Before transfer to the burn treatment center, the patient was treated with morphine, prednisone, and diphenhydramine.

Initial assessment after transfer noted a heart rate of 102 beats per minute with respirations at 18 per minute and a rash involving 48.5% TBSA consistent with TENS.² The arms and chest now demonstrated bullae and the patient, due to inadequate fluid management, treatment with an opiate, and sedation with a benzodiazepine, became hypotensive with a pressure of 106/42 mm Hg. Painful oropharyngeal mucosal involvement with scattered blisters extended proximally to distal lower extremities. Due to the late presentation of the patient to our burn treatment center, skin biopsy was not recommended or obtained by dermatology. Late biopsies of SJS and TENS often only demonstrate nonspecific epidermal necrosis. The chest wounds were covered with Conformant® (Smith & Nephew Wound Management, Largo, FL), and the blisters on the buttocks were covered with Duoderm® (ConvaTec, Princeton, NJ). The patient also experienced desquamation on her bilateral breasts which progressed further over the next 24 hours and conjunctival sloughing on day 21. By day 25, weeping lesions now involved all four extremities; however, improvement in renal function was noted with a serum creatinine of 2.6 mg/dl. On postexposure day 26, the

patient was advanced to an oral diet and serum creatinine was now 2.1. Cultures of the wounds also remained unremarkable. Vital signs throughout the admission were unremarkable with the exception of mild hypertension. She was discharged after 8 days of treatment with a serum creatinine of 1.9 mg/dl and followed up at the outpatient burn wound care center. By applying the Naranjo adverse drug reaction assessment tool, a score of 5 was noted, and thus this adverse event was considered to be of probable association with amlodipine.¹⁴ The SCORTEN on admission was 4.

DISCUSSION

Medication-induced SJS is frequently caused by anti-epileptic medications, fluoroquinolones, and trimethoprim sulfamethoxazole; however, with a larger list including other commonly used medications. The appearance of maculopapular rash often warrants rapid discontinuation of suspected medications; however, progression to SJS or TENS must also be considered. During the cough and colds season, the non-specific complaints for the first 8 to 12 days preceding the rash, such as itchy eyes and sore throat, are often attributed to an upper respiratory tract infection.²

Changes in distribution volume and clearance place elderly patients at risk for adverse drug reactions. Looking at the area under the serum concentration-time curve (AUC) as an "exposure time" also demonstrates a higher risk among elderly patients, consistent with increased reports of adverse effects of medications. For amlodipine, the AUC increases in the elderly by 40 to 60% due to subtle changes in hepatic and renal function.¹⁵ Renal dysfunction impacts the AUC of this medication even though the drug has minimal renal clearance. Although the American Hospital Formulary Service (AHFS) recommends reducing the average starting dose to 2.5 mg per day to elderly patients with renal impairment, there is no evidence that SJS or TENS is related to increased serum concentrations of amlodipine.¹⁵

Treatment of progressive dermatotoxic reactions remains largely supportive; however, early withdrawal of the causative medication and transfer of patients with extensive skin surface involvement to a burn treatment center or a facility familiar with the treatment of large open wounds remains a central part of patient management. Recent literature has shown that burn treatment centers are appropriate units for the management of SJS and TENS patients because of their skills in managing large open wounds.^{5,7,9} Discharge counseling for patients admitted with SJS or TENS includes both recommendations to avoid medications known to cause serious skin rashes and to

inform physicians that they have a history of drug-induced epidermal desquamation. Antiepileptic drugs have shown common structures associated with specific adverse drug reactions, including SJS and TENS.¹⁶

Although a case of SJS had been reported to the manufacturer's adverse reaction department (Pfizer Product Information, personal communication, June 5, 2007), this case represents, to our knowledge, the first published case of SJS or TENS involving amlodipine.

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September, 5, 2013

Dear Steve:

I am submitting the manuscript which I spoke to you about at the most recent ABA meeting in Palm Springs. Though I have retired, I am still working with the group to complete the publication of our results of studies and poster presentations. I am also working with my replacement at Crozer-Chester to get her going to assist Megan with research efforts.

This manuscript represents our very positive experience with the APRV mode in managing patients with severe inhalation injury. Early in the study, all patients were put on APRV after failing other modes of ventilation as salvage. As the burn surgeons became more comfortable with APRV it was used earlier in patient management prior to progression to respiratory failure with other modes. The manuscript reflects our experience with APRV and provides some insight as to why we seem to have been more successful than others in using this mode in severe inhalation injury. We look forward to reviewer comments and feel that this manuscript is appropriate for Burns.

I no longer have a Crozer-Chester Medical Center email address but I can be reached at Bhackerperson@aol.com which is a separate address from the family. You had asked if I would be willing to continue to review manuscripts. I would be available at the email address to do so.

Sincerely,

Bruce H. Ackerman, Pharm D

*Reviewer Suggestions

Suggested Reviewers

Lynn Solem, MD

Richard Cartotto, MD

Conflict of Interest statement – Burns – APRV manuscript

All of the authors were integral in the development of this study and all of the authors contributed to the development of the protocol, discussion of the resulting data collection, and all authors reviewed the manuscript prior to the submission of the final draft to Burns. The manuscript represents a multidisciplinary study in which specific health care professionals contributed their specific professional expertise to the manuscript under review.

None of the authors of this manuscript have knowledge that they own stock in medical companies manufacturing or marketing ventilators or ventilator disposable equipment. None of the authors provide in-services or talks on ventilatory support modes paid for or supported by manufacturers of ventilatory equipment or disposable supplies. None of the authors have received funding for research with APRV or other modes of ventilatory support and this current study was not funded, supported, nor assisted in any way by manufacturers of ventilatory equipment or disposable equipment. The current manuscript is an original manuscript written, revised, and reviewed by all the authors with no review by any manufacturer of ventilators or disposable ventilator equipment. There are no “ghost writers” or undisclosed authors of this manuscript. There are no undisclosed authors or persons assisting in the writing of this manuscript. None of the authors constitute persons to be labeled as “acknowledgements” in this manuscript.

This manuscript represents original research that has not been partially or wholly submitted for review in any other medical publication nor has any portion of the research been published other than as an abstract at the ISBI 2012 meeting. This manuscript has been submitted to Burns representing the total research experience with no partial submissions of data from this study to other journals.

With the exception of Mary Lou Patton, MD, none of the authors are members of the board of a pharmaceutical company or wound product manufacturer. Dr. Patton sits on the Board of Moelycke Wound Care and has been in the past the principal investigator for a multi-center study funded by Moelycke focused on their product MepitelOne™ in burn patients. This study has been completed, data have been analyzed, and I believe has been submitted for publication by Moelycke. Dr. Patton has spoken concerning this study at wound meetings and has received compensation for her travel. It is my understanding that this is her only conflict of interest and that this would have no impact on her as an author of a paper on APRV mode of ventilation.

Sincerely

Bruce H. Ackerman, PharmD

Retrospective Review of Inhalation Injury Patients Receiving APRV versus other Ventilator Modes for Respiratory Distress Syndrome or Acute Lung Injury in the Nathan Speare Regional Burn Treatment Center

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Abstract

Airway Pressure Release Ventilation (APRV) represents one of several ventilatory options for patients with inhalation injury. Over a period of five years, 274 of 1826 patients were admitted to our verified Burn Treatment Center with bronchoscopy-confirmed inhalation injury. This represented 15% of our admissions for the study period. For 78 of the 274 patients, enrollment criteria were met and complete medical records were available. For 40 of these 78 patients, APRV was used in management of inhalation injury with about half having failed prior mechanical ventilation modalities. The remaining 38 patients met the criteria for enrollment and had medical records available, but were treated with other mechanical ventilation modes. Gender was equally distributed between the two study groups and there was no significant difference in age or length of stay. The APRV group on average had greater ISS scores ($T = 3.97$; $p < 0.05$) and greater number of days on the ventilator ($T = 2.12$; $p < 0.05$). Organisms isolated from sputum were equally distributed between groups ($X^2 = 17.92$; $p > 0.05$) as was the antibiotic selection in treatment ($X^2 = 20.37$; $p > 0.05$). The non-APRV group had smaller burn injuries ($T = 5.06$; $p < 0.05$). Thus there was a survival difference between the two groups ($X^2 = 13.84$; $p < 0.05$) favoring the non-APRV patients. All patients had $PO_2:FiO_2$ ratios (P:F ratios) < 200 at the start of mechanical ventilation. Time to P:F ratio > 200 was 49.2 ± 63.9 hours in APRV patients; however, in the second half of the study period this was reduced to an average of 10.1 hours. The average time on APRV 10.8 ± 8.4 days (IQ range 3 to 17.8 days) Among APRV non-survivors P:F ratio > 250 was attained in $> 65\%$ of patients. Comparison of the first 2.5 years P:F ratio > 200 of 33.2 hours to the 10.1 hours in the latter period documented greater comfort with

clinicians using APRV and choice of APRV as the initial mechanical ventilation mode for inhalation injury. These data support the utility of APRV in management of inhalation injury and demonstrate that greater familiarity and comfort with APRV over time will decrease the time on APRV and facilitate weaning from mechanical ventilation.

Introduction

Inhalation injury remains a major cause for death following burn injury. Patients with inhalation injury require larger fluid resuscitation volumes exceeding the calculation of resuscitation volume according to the Parkland formula. [1-3] The extent of parenchymal tissue damage is poorly demonstrated by chest x-rays, but is clearly noted by CT scan. The State of the Science Conference in 2006 included discussion of inhalation injury[4] and what was currently known, and its management. Inhalation injury occurs in approximately 20 to 35% of patients admitted for burn care.[1,2 4-8] Inhalation injury as a lung damage continuum represents: 1) inhalation of hot gases damaging the upper mucosa, 2) carbonaceous soot deposition in the bronchioles and alveoli, 3) deep inhalation of toxic gases causing damage, dysfunction, and apoptosis of alveolar cells,[2,9] 4) polymorphonuclear cell invasion of the alveoli [2], 5) local edema and swelling, 6) augmentation of lung tissue perfusion and lymphatic flow, 7) shunting of blood due to atelectasis, and 8) inactivation of pulmonary surfactant.[2,4]

The diagnosis of inhalation injury requires history of closed space thermal injury, presence of stridor, visible soot in the respiratory tract, and inflammation, blisters, and swelling of the respiratory mucosa as observed during bronchoscopy within 48 hours of injury.[2] Bronchoscopy represents the standard for evaluation of inhalation injury and allows for the direct visualization of the upper respiratory tract. Bronchoscopy does not provide evidence for lower airway inhalation injury. Chest x-rays and other readily available tests do not provide a clear picture of injury to the lower respiratory tract either.[10]

Pulmonary edema and interstitial fluid accumulation following inhalation injury were reported by Holm et al [5] who demonstrated no correlation between fluid resuscitation volume and extravascular lung water. This finding questions the presumption that capillary leak also “spills over” to the lung tissue. Ventilation modes have been selected in the past presuming this “spill over” and the need to increase pressure in the alveoli to reverse this “fluid leak.” APRV ventilation allows for greater elimination of carbon dioxide (CO₂) and encourages recruitment of collapsed alveoli.[11,12] For the inhalation injured lung, sustained pressures combined with permissive spontaneous breathing allow for reversal of the damage associated with inhalation injury and ARDS.[11] APRV differs from other ventilation modes in that it allows spontaneous breathing thus improving diaphragmatic function. APRV steadily improves ventilation over time by these recruitment processes.[10,11] Consistent with the processes involved with inhalation injury, APRV supports the inflamed and injured lungs while allowing the lung to resolve its dysfunction with minimal ventilator-associated injury. Ventilator weaning from APRV was evaluated by several criteria including the rate to tidal volume in liters and the PaO₂ to FiO₂ ratio (P: F ratio).[1,2,13-16]

This retrospective study evaluated the efficacy of APRV ventilation in patients suffering inhalation injury. Following IRB approval, charts of patients from October 1, 2004 to October 31, 2009 who required ventilator support for suspected inhalation injury were retrospectively reviewed. Chest x-rays with infiltrates were assessed for cardiac causes of infiltration using echocardiogram reports noting left ventricular wall motion and estimates of the left ventricular ejection fraction. Chest x-ray findings with non-

cardiac disease-associated infiltrates were necessary for inclusion in this study. Some patients required a CT scan of the chest within 48 hours of admission. This data was also reviewed to assess parenchymal lung tissue damage. Fluid resuscitation needs were assessed and were consistent with other reports of greater fluid needs for patients with inhalation injury and burns.[3] Serial arterial blood gases prior to and following initiation of APRV or other ventilator support mode were reviewed and collected for changes in P: F ratio. The total fluid resuscitation needs at 48 hours were recorded as were vital signs, and urine output. Evaporative water loss per hour was calculated using the standard formula $25 + \text{total burn surface area involvement} \times \text{body surface area}$ and daily insensible fluid loss was calculated and compared to input and output differences.

This retrospective study sought to answer several questions about the use of APRV in inhalation injury patients:

1. Does APRV ventilation provide distinct advantages over other ventilator modes?
2. Is our success with APRV a reflection of our APRV protocol or specific ventilator used?
3. Does APRV increase the P/F ratios faster than conventional ventilation?
4. Does APRV result in any meaningful difference in outcome?

Methods:

All patients with suspected inhalation injury admitted during the study period from October 1st 2004 to October 31st 2009 were retrospectively reviewed. All enrolled patients demonstrated an inhalation injury that was documented by bronchoscopy within 24 hours of admission. Patient data collected for this study included arterial blood gas reports, vital signs, respiratory tract infections and pneumonia, duration of ventilator support, complications of respiratory support (i.e. pneumothorax, etc.), and survival as a result of the use of APRV or other modes of acute ventilatory support.

All enrolled patients required ventilator support within 24 hours of admission. Evidence from the bronchoscopy report obtained during first 24 hours of admission including assessment of the need for continued intubation was necessary for enrollment. Patients receiving APRV were retrospectively identified and additional patients receiving other ventilator modes during this study period with the same study entry criteria were also evaluated as a comparison group for this study. Sufficient patient medical record information was available for all patients identified for enrollment and no patients were excluded from analysis due to inadequate clinical data.

Assessment of Bronchoscopic findings: Criteria published by Endorf et al [1] were used to assess inhalation injury.

Inclusion criteria: All patients with bronchoscopy verified evidence of inhalation injury and requiring ventilatory support for more than 24 hours post-injury between October 1, 2004 and October 31, 2009 were included in this study.

Exclusion criteria: Patients with Stage D congestive heart failure, end stage renal disease, or other disease state that would have compromised aggressive fluid resuscitation were excluded from the study. In addition, patients noted during screening to have HIV disease with a history of PCP were excluded. The definitive assessment for left ventricular dysfunction is Swan-Ganz catheterization and collection of hemodynamic parameters. This central catheter monitoring method has seen decreased use in intensive care over the past few decades and is no longer routinely used in our Burn Treatment Center. As a surrogate assessment of cardiac function, echocardiograms were used to assess left ventricular function and to estimate the ejection fraction. In this manner, cardiac causes of infiltrations were ruled out as cardiac in origin on the chest x-rays of patients being considered for enrollment. Patients taking cardiac medications for known cardiac dysfunction or for chronic fluid management were excluded from analysis.

Statistical analysis: Patients were initially stratified based on inhalation injury and percent total body surface area involvement. P:F ratios were compared using analysis of variance to determine if increasing total body surface area involvement or mode of ventilator support were different. Bronchoscopic reports were assessed as described by Endorf et al¹. Fluid needs were assessed as ml/kg/%TBSA and stratified by PaO₂:FiO₂ ratios above and below 250 and compared using the student's t-test. CT scan findings when obtained as clinically necessary and as part of clinical management to assess lower lung pathological changes.[15-17]

Baseline data collection: Demographic data included age, gender, total body surface area involvement, past medical history including tobacco use, non- tobacco smoking, and ethanol use. Exposure to cardiac medications such as adrenergic receptor antagonists, use of angiotensin converting enzyme inhibitors or angiotensin 2 receptor antagonists, use of more than 40 mg of furosemide orally per day, use of glitizones for management of diabetes, hydralazine or calcium channel blockade were also assessed in enrolled patients.

For the period of ventilator support, patient weight, fluid intake and fluid output were recorded daily. In addition, heart rate, blood pressure, temperature, white blood cell count, hemoglobin, hematocrit, platelet count, serum albumin, serum electrolytes, prealbumin, and any obtained C-reactive protein determinations were recorded from the patient medical record. Arterial blood gases data were collected from the computer laboratory reporting system. Ventilator mode, tidal volume, mean airway pressure, and FiO_2 were extracted from these reports. Blood transfusions, fresh frozen plasma, and albumin administration were recorded as well. Bronchoscopic findings were recorded as well as description of findings reported for CT scans, echocardiograms, cardiac catheterizations, chest x-ray reports, and measurements of central venous pressure.

Outcome measures: The principle outcome measure sought was the duration of ventilator support, complications of ventilator support, and patient survival among confirmed inhalation injury patients using APRV or other modes and the change in duration of APRV as a reflection of “comfort” with this ventilatory mode was assessed.

Results

A total of 78 of 274 (28%) patients with inhalation injury met enrollment criteria for the time period between October 1, 2004 and October 31, 2009. A total of 40 patients meeting enrollment criteria had been managed with APRV and this population group was compared to 38 inhalation injury patients treated exclusively with other ventilator modes using the same entry criteria. Inhalation injury accounted for 15% (274 of 1826) of our American Burn Association approved admissions during the study period. Distribution of APRV versus other modes did not differ by gender between the two groups ($X^2 = 2.51$; $p > 0.05$). Student's t-test comparison between the two ventilator treatment groups for age was not significant. Burn size was smaller in the non-APRV patients ($T = 5.06$; $p < 0.05$) as was the ISS score ($T = 3.97$; $p < 0.05$) and number of ventilator days ($T = 2.12$; $p < 0.05$). Length of stay (LOS) though did not differ between groups ($T = 1.22$; $p > 0.05$). ISS scores greater than 16 differed markedly between the APRV and the non-APRV patient groups with 29 of 34 ISS score patients greater than 16 in the APRV group while only 22 of 37 non-APRV patients had ISS Scores greater than 16. Organisms isolated from sputum were equally distributed in both groups ($X^2 = 17.92$; $p > 0.05$) and antibiotic use likewise was equally distributed between the two groups ($X^2 = 20.37$; $p > 0.05$). Assessment of severity of illness by ISS score (see Table 1) suggested that the APRV patients were „sicker“ than those treated with other ventilator modes which is consistent with our experience. Early use of APRV was in patients that had already failed conventional ventilation therapy. Mortality was greater in the APRV patients ($X^2 = 13.84$; $p \ll 0.05$). The P:F ratio at the start of APRV ventilation was on

average 132.5 ± 39.3 with an intra-quartile range of 78.5 to 178. All patients had a P:F ratio < 200 .

One measurement of interest was the time to achieving a P:F ratio over 200 and for APRV patients this was 49.2 ± 63.9 hours (intra-quartile range 5.4 to 70.7 hours). The observed range in reaching these P:F ratio goals also reflected clinician comfort with APRV as a ventilator mode over time. For patients who expired while on APRV, the average number of days was 10.0 ± 8.4 days with an intra-quartile range of 3 to 17.8 days. Skew and kurtosis of the distribution warranted either removal of outliers or log transformation of the data. Log transformation resulted in near normalization of the distribution and values of 8.0 ± 2.5 days of ventilator support. This duration of APRV indicated that this ventilator mode provided sustainable ventilator support in this very ill and dying subpopulation. The use of APRV resulted in P:F ratios in the 200 to 250 range for more than 65% of the non-survivors again indicating that death was most commonly not due to ARDS itself. No one died of ARDS within 24 hours of being put on APRV.

As post-hoc analysis, data were divided approximately in half for the approximately 5 year time period studied. For the first time period of approximately 2 and one-half years when clinicians were learning how to use APRV, the time to achieving a P:F ratio > 200 was 33.2 hours on average among survivors while for the second approximately 2 and one-half year period at the end of this study period this time had reduced to 10.1 hours on average. This marked change in achieving a P:F ratio of > 200 reflected greater comfort with changing time and pressure parameters in treatment of the ARDS patients with APRV in the second half of the study period. It also reflected

the decision to more frequently choose APRV as the initial ventilator mode in patients admitted with inhalation injury.

Comparison of time to P:F ratio > 200 for the APRV patients versus conventional ventilatory support demonstrated comparable time to achieving this goal for APRV patients ($T = 0.011$ $p \gg 0.05$) for the entire five-year study period. Comparing the time to reaching this goal for the second half of the study periods compared with all five years of the conventional ventilation modes noted less time to achieve this goal in the APRV patients ($T = 2.05$ $p = 0.04$).

Discussion

APRV was initially described by Stock and Downs as a form of CPAP with intermittent pressure release providing a unique ventilator mode.[18] The management of inhalation injury represents a more complicated form of respiratory distress syndrome that has been managed by new modalities such as high frequency oscillatory ventilation (HFOV).[19-21] and airway release pressure ventilation. These two modes of ventilation share a common action in that they permit recruitment of injured lung, protection of injured lung, and increase lung function. Both modes are often used as rescue modes for severe ARDS[19] and this is consistent with our early use of APRV. Though there have been many ventilatory modes used for inhalation injury, little has been done to distinguish the various mode options for any reduction in the incidence of multiple organ failure, length of stay, long term mortality, long-term cognitive outcome, and reduced need for high benzodiazepine drip rates.[19-21] Bronchospasm, marked edema, and mucosal sloughing limit alveolar recruitment with HFOV. Gas trapping and excessive secretions also limit the success of HFOV in inhalation injury.[19] Clearly, comparisons of ventilatory mode will require standardization of ventilators and more consistently defined outcome measures.[20]

Generally ventilators are capable of controlling the pressure or the volume of air delivered.[21] Volume assured pressure support reduced the work of breathing. Switching from pressure control and back to volume control often reflects changes in lung compliance and increased airway resistance, the pressure of excess secretions, or other airway problems. Volume support modes depend on patient triggered respirations and are pressure limited and are thought to be ideal for patient weaning. Conventional

pressure support prolongs the inspiratory cycle time and makes it more difficult for the patient to exhale spontaneously. This leads to air trapping which limits the triggering of the ventilator by the patient in volume support modes with increasing air trapping and auto PEEP. As auto PEEP increases, patient-triggering of the ventilator is decreased. Airway pressure release ventilation provides the positive attributes of pressure support with the sudden release causing patient effort to exhale and provides a consistent tidal volume whether lung compliance increases or decreases.[21] The study by Kagan et al looked at DRG 504 in 107 greater than 10% total body surface area burn patients. These patients required an average of 19.5 ± 1.4 ventilation days. [3] This compares favorably with our data where non-APRV patients were ventilated for 14.5 ± 13.8 days versus 35.9 ± 31.4 days among APRV patients. Mortality was 32% in their study and 28% in our 78 patients. Length of stay was 43.8 ± 3.7 days in their study and 44.3 ± 33.3 days in our study. Total body surface area burns were $40.4 \pm 1.8\%$ which was more consistent with the $41.6 \pm 29.4\%$ in the APRV patients. Ninety-four of these patients required ventilatory support for > 96 hours. A second study looking at 258 consecutive patients noted increased fluid requirements in patients with inhalation injury and burns greater than 30%.[22] Two time periods were studied (1987 to 1996 and 1997 to 2006) with the second having more apparent inhalation injuries, with doubling of ventilatory support from 38% to 76% of patients due to initiation of ventilatory support prior to transfer and excessive pre-transfer fluid administration. Bronchoscopy was routinely done on inhalation injury patients after 1990. However, the number of patients that were intubated and put on ventilator support markedly increased after 1997. The authors suspected the routine use of bronchoscopy increased the use of mechanical ventilation.

This was also the time period for the development of the Trauma specialty in the Netherlands. Routine intubation of suspected inhalation injury with no clear bronchoscopic support increased in this latter period. These authors also suggest that excessive fluid administration prior to transfer to the burn center may also have impacted on the need for mechanical ventilation for patients ruled out for inhalation injury. The comparison of SIMV versus APRV and prone positioning was studied and demonstrated marked improvement in oxygenation. This paper looked at 24 APRV patients and compared them to 21 patients managed with SIMV. It was observed that there was improvement in both groups of patients during prone positioning as was demonstrable by improvements in the P:F ratio. After the second period of prone positioning, the APRV group demonstrated a significant improvement in P:F ratio when compared to SIMV. Our study also demonstrated a more rapid achievement of P:F ratio > 200 in our APRV patients and is consistent with the observations in this study from Finland.[23] These authors noted the spontaneous breathing of APRV and proposed that this made a difference when compared to SIMV. Ventilation perfusion mismatch and diaphragmatic tone more markedly improved with APRV.[23] In an earlier study, this group also noted improved ventilation- perfusion matching and decreased blood shunting in patients treated with APRV.[24]

APRV optimizes alveolar mechanics [11] and the spontaneous release permits greater CO₂ elimination by increasing the lung area involved in gas exchange. The release allows the lung to rapidly deflate when compared to other ventilation modes and this rapid deflation followed rapidly with re-inflation assures alveolar recruitment. These authors noted that ARDS is associated with decreased lung compliance and

conventional ventilation will increase the risk for lung over-distention and volu-trauma. They noted that ISS scores > 16 were most commonly associated with ARDS and for our study 29 of 34 patients (85%) with ISS score determinations had ISS scores in excess of 16. For the non-APRV patients 22 of 37 patients had ISS scores more than 16 (59%). APRV exploits the decreased compliance by causing greater elastic recoil when the pressure is released. With worsening ARDS, greater elastic recoil during pressure release increases CO₂ elimination. These authors also noted that less neuromuscular blockade (NMB) and sedation is needed with APRV when compared to other ventilatory modes.[11] This study was focused on trauma rather than inhalation injury patients, but did note that APRV favors oxygen delivery to the dependent lung which often has better blood flow. Maxwell et al noted no difference in length of stay, need for ventilatory support, or ventilator-associated complications between low volume ventilation modes and APRV.[12] They mentioned that the incidence of ventilator-assisted pneumonia (VAP) did not differ either in this very small study involving only 63 patients. They note that APRV is limited by no clearly developed weaning parameters. Yoshida et al noted APRV markedly improved collapsed lung using helical CT scans and attributed this to the spontaneous breathing permitted by APRV.[10]

The risk of VAP is of concern and a study by Walkey et al [25] looked at age, antibiotics used, need for NMBs, stress ulcer prophylaxis, and transfusion of blood as part of their analysis of patients. Delaying tube feedings for 48 hours and early tracheotomy made a difference in VAP. Patients on APRV had a delay in the onset of VAP and proposed that this mode may reduce the risk of VAP.[25] Habashi's paper in 2005, noted that CPAP provided inadequate CO₂ removal and tended to cause lung over

distention when compared to APRV.[26,27] Patients on APRV required only 40% of the sedation needed for other ventilatory modes and less breathing against the ventilator.[26] APRV permitted unrestricted spontaneous breathing and the periodic release augments CO₂ clearance. APRV allows for more appropriate redistribution of inflation stress with nearly uniform inflation counteracting the chaotic inflation processes in ARDS & acute lung injury (ALI) with other ventilatory modes.[27]

Most ventilatory support causes shear stresses in the lung with opening and closing of the alveoli induces cellular inflammation particularly in the absence of surfactant.[27,28] In order to prevent volu-trauma with low tidal volume ventilation, the PEEP must be increased to prevent de-recruitment and alveolar collapse. These processes cause increases in cytokines and diaphragmatic dysfunction. As such, APRV provides recruitment of injured lung, increased CO₂ elimination, and utilizes the edema and decreased lung compliance to facilitate CO₂ elimination. One issue though in comparing APRV to other modes of ventilation is that the ventilators providing the APRV mode option have shown differences among 6 ventilator models tested and that the differences in the function of the “floating valve” in the ventilator resulted in different results with APRV. Thus the controversy surrounding the use of APRV is further complicated by differences in ventilator delivery of APRV and thus differences in spontaneous breathing. One of the major benefits of APRV is alveolar recruitment and diaphragmatic stimulation benefits that are unique to this ventilatory mode.[29]

One of the limitations for this retrospective study was the demonstration “secular change” in the use of APRV. The experience for the first 20 APRV patients differed markedly from the latter 20 patients. As this was discussed, it was concluded that the

decision to start APRV earlier markedly improved the outcome of inhalation injury patients managed with this ventilatory mode. Reliance on documented echocardiography in order to rule out cardiogenic infiltrations on chest x-ray eliminated a number of the 274 initially screened patients. As with any retrospective study, the absence of complete medical records caused the elimination of subjects for analysis. The first 20 or so patients represented patients who had failed other ventilatory modes and were thus quite ill at the onset of APRV management. Survival was higher in the latter patients because clinicians considered APRV as initial therapy of inhalation injury with results more consistent with the experience of others treating inhalation injury with APRV.

Airway pressure release ventilation is associated with lower peak airway pressure, lower dead space ventilation, better oxygenation and reduction of left ventricular afterload compared to conventional modes of ventilation and can maintain spontaneous ventilation to a level comparable to that of ACVC. Spontaneous ventilation is relatively comfortable and well tolerated and occurs at any point in the ventilatory cycle. APRV uses almost constant airway pressure that not only facilitates alveolar recruitment but also sustains that recruitment once it has occurred and holds the lung open throughout the ventilatory cycle with using less sedation and avoiding neuromuscular blockade.

The ability to avoid paralytics and decrease use of sedation can result in fewer complications, lower ICU length of stay and decrease costs. Finally, ventilator-associated lung injury, which can result from both high- and low-volume lung ventilation, may be balanced and averted. Most studies show improvement in some clinical outcomes with APRV, however, none have reported a mortality benefit. The authors believe that future research will support the use of APRV as the mode of choice for

patients with ALI and ARDS.

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Table 1. Demographic data for 78 of 274 inhalation injury patients with non-cardiac infiltrates on chest x-ray admitted to a Burn Treatment Center

	Number (males)	Age	TBSA*	ISS [#]	Ventilator Days	Crude Survival (Percent)	LOS [@] (In Days)
All Patients	78 (50)	46.6 ±17.4	28.9 ±27.0 IQ range = 6.8 - 43	26.6 ±15.7	30.0 ±25.9 IQ range = 13-37	55 of 78 (70.5%)	44.3 ±33.3
Comparison Mode Patients	38 (21)	46.4 ±19.2	14.5 ±13.8 IQ range = 3.3 - 18.5	20.0 ±11.5	23.8 ±16.8 IQ range = 13 - 32.3	37 of 38 (97.4%)	39.6 ±26.4
APRV Patients	40 (29)	46.8 ±15.7	41.6 ±29.4 IQ range = 16.8 - 57.5	33.9 ±16.6	35.9 ±31.4 IQ range = 14 - 49.5	18 of 40 (45%)	48.7 ±38.7
	NS	NS	T = 5.06; p<<0.05	T=3.97; p <0.05	T= 2.12; p <0.05	X ² = P<<0.05	T = 1.22 p>0.05

* = Total Body Burned Surface Area; # = Injury Severity Score; @ = Length of Stay (patients are discharged directly from the burn treatment center).

ABSTRACT

INTRODUCTION: *Staphylococcus aureus* (SA) infections resulting from spread of this organism is of concern. Chronic carriers (CC) of MRSA are decolonized (D) to prevent the spread of MRSA. Many institutions screen for nasal MRSA carriage by culture or nasal swab (NS) MRSA PCR. D with mupirocin ointment is initiated in burn treatment center (BTC) American Burn Association criteria admissions to reduce the burden of MRSA in the environment. This may also prevent post-admission MRSA infections in BTC admissions. Our BTC D's all MRSA NS PCR positive patients (PT) as part of our infection control program. The impact of NS PCR D was investigated to determine the program's efficacy in preventing subsequent MRSA infection.

MATERIALS AND METHODS: Following IRB approval, the infection control department was contacted for surveillance data for 23 months from January 2010 to November 30th 2011 as the first part of an ongoing study evaluating screening since its initiation on August 1, 2006. Patient data were obtained from the medical record. PT data were analyzed with demographic statistics to determine normal distribution. Students' T-test was used for pair-wise comparison of data stratified by presence or absence of infection and further stratification by positive and negative NS MRSA PCR testing seeking significance of 0.05.

RESULTS: Our BTC admits approximately 450 - 475 PT per year. For the first 23 months we have identified 75 PT CC MRSA (11 PT with previous cultures and 46 PT with positive NS MRSA PCR). Thermal injury was involved in 70 PT and 5 PT were diagnosed with toxic epidermal necrolysis. For 18 PT the initial NS PCR was negative with conversion to positive with NS PCR in 7 PT and positive culture in 9 PT. Demographic data from stratification by NS PCR status was uninformative. Stratification by MRSA positive and negative isolation noted a difference in length of stay ($p < 0.05$) and total body surface area burn ($p < 0.05$) for MRSA culture positive patients. MRSA positive cultures were obtained in 36 PT (48%) for which erythromycin-clindamycin sensitive (ECS) MRSA was at least once isolated in 20 of these 36 PT. Demographic analysis of NS PCR status for both infected and non-infected patients was uninformative.

DISCUSSION: NS MRSA PCR does not distinguish between ECS MRSA and hospital acquired MRSA. It was of interest that 20 of the 36 PT with positive MRSA culture had at least one isolate of ECS MRSA indicating likely non-nosocomial acquisition. Assessment of the D program suggests that D helped prevent positive MRSA cultures in 16 of 31 admissions to the BTC with NS MRSA PCR positive screening.

INTRODUCTION

Infection with MRSA in the past was considered 'nosocomial' and thus many hospitals screen patients prior to admission to document pre-admission MRSA carriage. The risk of subsequent infection in patients with nasal swab (NS) PCR positive (POS) results versus NS PCR negative (NEG) patients is of interest as well as the presentation of ECS MRSA that is often coming from the community rather than the hospital environment. This study investigated the use of NS PCR as a screening tool to prevent MRSA infection in burn center admissions. For those patients who were PCR POS on admission, decolonization with mupirocin potentially prevented later MRSA infection.

METHODS AND MATERIALS

Following IRB approval, charts were retrospectively reviewed for NS PCR status. NS PCR obtained for all burn center admissions over a 23 month period were reviewed (Jan 2010 to Nov 2011). 66 of 826 PCR screened patients had NS PCR POS or POS cultures and 11 were known MRSA 'carriers'. Demographic data for these 77 patients are provide in **Table 1**. 18 patients were initially PCR NEG, 11 patients were known carriers, and 48 patients were PCR POS. These 48 MRSA PCR POS patients were decolonized. Chronic carriers were not decolonized. Routine cultures were collected for these 77 patients with the focus on isolation subsequent MRSA from sputum, central venous catheters, blood, and wounds.

Table 1. Average Initial MRSA NS PCR or Carrier Status in 77 Patients

	Age in Years	LOS in Days	%TBSA
PCR NS NEG (N = 18)	39.9 ±26.3	30.8 ±28.7	17.3 ±17.2
MRSA CARRIERS (N = 11)	34.3 ±20.7	36.5 ±43.7	17.3 ±20.6
PCR NS POS (N = 48)	36.7 ±23.6	12.2 ±16.3	12.6 ±19.3
ANOVA	F = 0.211; P>0.05	F = 6.500; p <0.05	F = 0.467; p >0.05

RESULTS

MRSA chronic carriage (n = 11) was 1.6% and NS PCR POS screened burn center patients. ECS MRSA was only acquired in patients. All of these initially PCR NEG patients (n = 18) became 9) or NS PCR (n = 9) while only 17 of 59 (29%) NS PCR POS patients had positive cultures. For the 48 PCR POS MRSA patients, 14 acquired ECS MRSA. 34 did not acquire MRSA infection after mupirocin decolonization (40% of 48). MRSA had a mean burn size of 19.2% vs. 8.9% for those who did not acquire MRSA. 17 of 38 (45%) patients had at least one ECS MRSA culture. 38 of 48 PCR POS MRSA cultures or repeat nasal PCR following screening (9 of 38) PCR NEG patients who converted to POS during their admission. 3 of 6 had POS wound cultures, and 9 had PCR POS NS prior to discharge. 11 patients converted to MRSA POS with 5 having ECS MRSA. Of 11 MRSA NS PCR POS and 11 known MRSA carriers, 28 patients (45%) prior to discharge NS screening. For the 48 MRSA PCR POS patients, decolonization potentially prevented subsequent MRSA infection in 31 (64%). 11 MRSA carriers were not decolonized and 5 of these 11 carriers had ECS MRSA POS cultures (45%).

CONCLUSION

MRSA was found in 9.1% of admitted burn patients. ECS MRSA was only acquired in PCR POS burn patients. When compared to the 27 patients who acquired MRSA but did not, it was noted that age did not differ, but there was a higher burn size. Decolonization potentially prevented subsequent MRSA infection in 64% of patients to be MRSA NS PCR POS on admission.

Abstract

Calcific Uremic Arteriolopathy-A Combined Aggressive Conjoint Nephrology/Burn Surgery Management

Calcific uremic arteriopathy(CUA), commonly called calciphylaxis, is a systemic calcification of arterial medial and soft tissues causing various quantities of soft tissue destruction.

The incidence of CUA has been increasing in recent years due to an increased awareness among physicians (Wang, K.L., et al *Kidney Int.* 70.7 [2006]: 1196) as well as aggressive treatment of hypocalcemia with vitamin D in chronic kidney disease patients. It has been estimated that 1% of end stage renal disease patients develop CUA each year increasing in prevalence to 4% in dialysis patients yet more common post renal transplant failure. Mortality, most commonly is a result of wound infection that may approach 80% (Scully, RE et al. *NEJM* 2001; 345; 1119)

We present a case of CUA in a 32 year old female patient post renal transplant failure requiring subsequent dialysis diagnosed with hyperparathyroidism and treated initially with cinacalcet (sensipar). Despite this therapy her parathyroid hormone level remained high (3110 pg/ml) and she underwent parathyroidectomy. Over the subsequent 4 weeks she developed dark, painful ulcerating lesions of her breast and abdomen. She was treated on the medical-surgical floor by the nephrology service with daily silvadene dressings. Development of new torso lesions prompted the addition of 25g sodium thiosulfate daily to her regimen. Because of deterioration of her wound status and severe pain associated with the wounds the Burn Service was asked to help manage the patient.

Her treatment consisted of multiple debridements with temporary closure utilizing a silver nylon dressing in conjunction with a negative pressure device. The wounds were ultimately closed with a two stage Integra® grafting system or primary closure where possible. Pain was controlled as typical in our burn center with analgesics titrated to the degree of pain that the patient was experiencing. The grafted wounds healed well as did the wounds closed primarily and the patient was discharged home.

This experience has prompted us to formulate a treatment paradigm for patients with CUA. We believe that because wound infection is the primary cause of death appropriate and aggressive surgical wound management as well as adequate pain control is absolutely necessary. However, we realize that aggressive renal replacement and management is also indispensable to halt progression of the presenting lesions as well as preventing development of new areas of calcification and necrosis.

INTRODUCTION

It is estimated that 1 to 4% of hemodialysis patients per year will develop systemic calciphylaxis.^{1,2} Because this is a rare and poorly understood phenomenon, diagnosis may be delayed or missed. With increasing numbers of hemodialysis-dependent patients systemic manifestations of calciphylaxis are becoming more common.² The etiology of calciphylaxis is not entirely known. Pathologically, calcium deposits are seen in the fat, subcutaneous tissue, dermis, epidermis, and vascular system causing ischemia and subsequent necrosis. Mortality, typically from infection, may approach 80%.³ Phosphorous binding medications are often prescribed as first line treatment which may result in further elevation of serum calcium levels. Newer systemic therapies such as sodium thiosulfate show promising results. Surgical interventions attempt to correct the primary physiologic alterations along with controlling resultant local cutaneous complications. Various treatment recommendations have been suggested without a uniform consensus for management. We present a patient successfully treated with a combination of medical and surgical therapy.

CASE PRESENTATION

Our patient was a 30 year old female diagnosed at 13 with medullary cystic kidney disease. She underwent renal transplant at 22 years of age. Subsequently she had transplant rejection and resumed chronic hemodialysis.

She was admitted to the hospital complaining of painful lesions on her breast and abdomen. Her parathyroid hormone level was elevated and a parathyroidectomy was performed. The abdominal wounds were biopsied and sodium thiosulfate therapy was initiated.

The lesions on her breast and abdomen were painful, covered in thick eschar with bleeding at the wound edges. She underwent excision and debridement to the level of viable tissue. A vacuum-assisted dressing (VAC) was applied. At subsequent VAC changes a silver nylon dressing was applied. All pathology samples revealed dystrophic calcifications and focal necrosis. Additional surgery included debridement and Integra placement. Second stage split thickness skin grafting (2:1 mesh) over Integra dermis was performed. Two abdominal wounds were debrided and closed primarily without tension. All wounds healed well and the patient was discharged home. Follow up in the office did not reveal further lesions and the patient was pain free.



DISCUSSION

Calciphylaxis is a rare but disfiguring and potentially lethal complication of end-stage renal disease. This phenomenon was first described by Selye in 1962.⁴ Initially wounds were left to heal primarily or autoamputate commonly resulting in sepsis and death. While the exact etiology is unknown, pathology demonstrates dystrophic calcium deposits resulting in painful lesions.

The underlying renal disease must be controlled by the combination of hemodialysis and medical therapy to achieve acceptable calcium and phosphorous levels. Parathyroidectomy has been advocated in patients with calciphylaxis. Although not all patients with secondary hyperparathyroidism develop calciphylaxis, those who do typically benefit from parathyroidectomy.

Although medical treatment is necessary for systemic control and prevention of disease progression, surgical therapy is crucial for control of cutaneous manifestations. The extent of the calcium deposits and subsequent necrosis dictates available therapies. As lesions enlarge excision and primary closure may become impossible. The wounds eventually become the nidus for lethal infection and may not be survivable. Methods to accelerate closure are important. Hyperbaric oxygen may be employed and this modality has proven useful in a small published series.⁵ Vacuum-assisted closure has been suggested to debride necrotic tissue and remove local soluble inflammatory mediators.⁶ Emohare et al. described granulation and contraction when used on calciphylaxis wounds after debridement.⁷ Primary closure is ideal only if the wound is adequately debrided and the closure is tension free because the already compromised tissue may easily necrose. Skin grafting has been employed to close wounds but may leave additional wounds. Beless, et al, suggest using a bilayered skin equivalent (Regranex) as a viable alternative eliminating the creation of a donor site.⁸

We employed a combination of previously described therapies resulting in complete resolution. Medical therapy had been exhausted when our patient was transferred to the Burn Unit. Initial serial debridements provided a clean wound bed for coverage. The VAC maintained a clean wound while promoting granulation tissue. A synthetic biological dermis, Integra, was utilized as an adjunct to wound closure. The abdominal wounds were amenable to primary closure without tension. By employing multiple techniques the patient recovered well in a relatively short time period proving that a combination of surgical approaches results in a faster recovery.

Early recognition and intervention are crucial to the treatment of calciphylaxis. A multidisciplinary approach is necessary. The underlying disease and subsequent metabolic derangements must be addressed along with prompt management of wounds as mortality often results from infection.

CONCLUSIONS

A combination of treatment technologies should be employed. Medical and surgical interventions should be used to achieve the best results. A heightened suspicion is necessary for early recognition and intervention is key to prevent mortality. Once cutaneous manifestations are identified, early debridement should be obtained. If debrided early, the defect may be closed primarily although with caution as this tissue is fragile. Primary closure should attempt to achieve disease free margins. Because this is a systemic process and edges may be involved, a wide margin of disease-free tissue should be achieved. After achieving a healthy wound bed, primary closure is the goal.

We advocate an aggressive multidisciplinary approach to the treatment of calciphylaxis. Wound care should utilize a combination of surgical and medical closure of wounds. Medical therapy adds to the management of lesions.

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Catechol-*O*-Methyltransferase Genotype Predicts Pain Severity in Hospitalized Burn Patients

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Increasing evidence suggests that stress system activation after burn injury may contribute to burn-related pain. If this is the case, then genetic variations influencing the function of important stress system components, such as the enzyme catechol-*O*-methyltransferase (COMT), may predict pain severity after thermal burn injury. The authors evaluated the association between *COMT* genotype and pain intensity in 57 individuals hospitalized after thermal burn injury. Consenting participants at four burn centers were genotyped and completed daily 0 to 10 numeric rating scale pain assessments on 2 consecutive days including evaluation of waking, least, and worst pain. The association between *COMT* genotype and individual pain outcomes was calculated using a linear mixed model adjusting for sociodemographic and burn injury characteristics. Overall pain (combination of least, worst, and waking pain scores) was significantly higher in patients with a *COMT* pain vulnerable genotype (6.3 [0.4] vs 5.4 [0.4], $P = .037$). Individuals with a *COMT* pain vulnerable genotype also had significantly higher “least pain” scores (3.8 [0.5] vs 2.6 [0.4], $P = .017$) and significantly higher pain on awakening (6.8 [0.5] vs 5.3 [0.4], $P = .004$). Differences in worst pain according to genotype group were not significant. *COMT* pain vulnerable genotype was a stronger predictor of overall pain severity than burn size, burn depth, or time from admission to pain interview assessment. These findings suggest that genetic factors influencing stress system function may have an important influence on pain severity after burn injury. Further studies of genetic predictors of pain after burn injury are needed. (J Burn Care Res 2012;33:518–523)

Despite major advances in burn care, ~50,000 patients admitted to U.S. burn centers each year¹ experience substantial pain during hospitalization.^{2,3} It is often assumed that burn pain intensity is primarily

determined by injury characteristics such as burn size and depth. However, available data indicate that burn characteristics are not strong predictors of burn-related pain.^{4–6} This suggests that other as

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yet unidentified factors may play an important role in determining the pain experience of burn patients. The identification of such factors may create new opportunities to improve burn care.

Increasing evidence suggests that stress response system activation after burn injury may contribute to burn-related pain. In addition to causing direct tissue damage, a burn injury is a potent stressor which activates the sympathetic nervous system and adrenomedullary hormonal system, resulting in the release of catecholamines.⁷ Results of both animal and human studies have demonstrated that catecholamine levels influence pain sensitivity.⁸⁻¹³ If this is the case, then genetic variations affecting catecholamine levels may predict individual variations in pain severity after burn injury.

One stress system component influencing catecholamine levels is the enzyme catechol-O-methyltransferase (COMT). COMT is the primary enzyme that metabolizes catecholamines, including epinephrine, norepinephrine, and dopamine.¹⁴ Genetic variations in the *COMT* gene (*COMT* diplotype) influencing *COMT* enzyme function have been found to predict acute pain sensitivity in experimental settings.¹⁵ In addition, classifying patients by *COMT* diplotype into those with or without a “*COMT* pain vulnerable genotype” has been shown to predict musculoskeletal pain severity and psychological distress after minor injury.¹⁶ However, to our knowledge, the potential contribution of genetic variations influencing the function of important stress system components such as *COMT* to pain after major injury has never been examined. In this study, we examined the association between *COMT* pain vulnerable genotype and pain intensity among patients admitted to the hospital after thermal burn injury. We hypothesized that hospitalized burn patients with a *COMT* pain vulnerable genotype would experience increased pain in comparison with those without this genotype. In addition, we compared the strength of association between *COMT* genotype and acute burn pain with the strength of association between several commonly assessed burn injury characteristics and acute burn pain. Because of increasing evidence that individual neurobiology has an influence on pain outcomes comparable to/greater than injury severity,¹⁶ we hypothesized that *COMT* genotype would have an influence on pain as great or greater than characteristics of the burn injury.

METHODS

Patients presenting to four burn centers (Jaycee Burn Center, University of North Carolina, Chapel Hill,

NC; The Burn Center, Washington Hospital Center, Washington, DC; Wake Forest University Baptist Burn Center, Wake Forest, NC; Nathan Speare Regional Burn Treatment Center, Upland, PA) within 72 hours of thermal burn injury between June 2009 and January 2011 were evaluated for study eligibility. Patients who were clinically unstable or who had coincident nonburn injury were excluded, as were prisoners; pregnant patients; patients with intentional injury; patients with a psychotic disorder; non-English-speaking patients; and patients with hepatic failure, renal failure, or a history of chronic opioid use (defined as ≤ 20 mg/d of oxycodone or equivalent). Also, because patients in this observational study were subsequently to be evaluated for participation in a randomized controlled medication trial, patients with $>20\%$ TBSA burn; patients with an estimated hospital stay of <5 days or >40 days; patients with greater than first-degree atrioventricular block; patients taking a β -adrenergic antagonist medication; and patients with asthma, diabetes, coronary artery disease, and congestive heart failure were also excluded. Patients were also excluded who in the opinion of the investigators would not provide reliable data. Local institutional review board approval was obtained from all study site institutional review boards.

Eligible patients were approached by research staff for study participation within 48 hours of burn center admission. Written informed consent was obtained from all participants. Study participation included blood sample collection for genetic analysis and completion of daily pain symptom interviews on 2 consecutive days after enrollment. During each daily pain symptom interview, participants were asked to rate their worst pain, their least pain, and their average pain over the past 24 hours, as well as their pain upon waking. Each pain assessment was performed using a verbal 0 to 10 numeric rating scale, where “0” was defined to the patient as “no pain” and “10” as “pain as severe as it could possibly be.” A verbal numeric rating scale was used because it has been validated as a substitute for the visual analog scale in acute care settings¹⁷ and because it does not rely on upper extremity use to make a precise mark on a scale. Daily pain symptom interviews that included the above assessments were performed on 2 consecutive days, beginning on the day of enrollment.

For study analyses, our initial intention was to combine the two ratings of daily average pain for each patient (one rating each day obtained on 2 consecutive days). However, as daily pain symptom interviews were being conducted, it was observed that patients sometimes provided an “average” pain rating greater than their worst reported pain or less than their least

reported pain. These observations, together with the high degree of educational disadvantage in this population, led us to appreciate that our study question ("Please rate your average pain during the last 24 hours...") was poorly designed for the study population and (because of misunderstanding) did not yield valid data. Because of this, instead of using average pain, we took advantage of the multiple different pain assessments available within each individual (waking, worst, and least pain on 2 consecutive days) and created a measure of overall pain burden using linear mixed modeling described below. This measure of overall pain was used as the primary outcome measure for all analyses. Mean scores for waking, worst, and least pain over 2 days were also obtained from this model.

Study participants received analgesics as per standard study site burn care; no changes were made to the pain treatment of study participants. Information regarding medications received during the 2-day study period was extracted from the medical record. For each opioid analgesic medication, total dose received during the 2-day study period was calculated and then multiplied by a conversion factor referenced to a 30-mg dose of morphine.¹⁸ These doses were then summed to provide the total opioid dose (in morphine equivalents) received by the patient during the 2-day study period. Benzodiazepine conversions were similarly calculated using a 10 mg diazepam reference.¹⁹ Demographic information was obtained during the initial patient assessment via standardized questionnaire. Information regarding patient burn characteristics was obtained from the medical record.

Blood samples were obtained for genetic analysis using an EDTA Vacutainer collection tube (BD, Franklin Lakes, NJ). DNA was purified from whole blood samples using the QIAamp DNA Mini Kit (QIAGEN, Valencia, CA) on the QIAcube (QIAGEN), as per manufacturer's instructions. Genotyping was performed using a TaqMan Allelic Discrimination Assay for rs4818 on the Bio-Rad CFX96 Real-time PCR Detection System (Bio-Rad, Hercules, CA) at either the University of North Carolina (Chapel Hill, NC) or Washington Hospital Center (Washington, DC). Patient DNA samples were genotyped together with six HapMap CEU DNA samples (two of each genotype) and two "no template" control samples.

When multiple disease susceptibility variants occur in the same gene, the overall functional state of the gene may not be easily deduced from information regarding a single-nucleotide polymorphism.²⁰ For this reason, we used a haplotype-based approach to examining *COMT* variants. In a previous study,

three haplotypes located in the central *COMT* locus accounted for approximately 96% of all haplotypes in this region and were associated with variations in pain sensitivity¹⁵ and posttraumatic pain.¹⁶ One of these haplotypes, the "low pain sensitivity haplotype," codes for high *COMT* enzyme activity and is associated with relatively low pain vulnerability (ie, is protective against pain).¹⁵ As in a previous study,¹⁶ we defined patients with no copies of this low pain sensitivity haplotype as having a "*COMT* pain sensitive genotype." Patients with a *COMT* pain sensitive genotype were identified by genotyping single-nucleotide polymorphism rs4818, because approximately 95% of individuals with a CC genotype at rs4818 have a *COMT* pain sensitive genotype.¹⁵

Statistical analyses used linear mixed modeling to evaluate the association between *COMT* pain vulnerable genotype and pain outcomes. Six pain measurements (waking, worst, and least pain for days 1 and 2) for each individual were entered into the model as a correlated outcome variable. The correlations between pain measurements within each individual were taken into account by specifying nested random effects for intercept. The measure of overall pain was obtained as an adjusted least square mean pain score incorporating waking, worst, and least pain for days 1 and 2. Mean scores for waking, worst, and least pain over 2 days were also obtained from this model. Age, gender, TBSA, burn depth, and time from admission to pain assessment were considered as important covariates and included in the model. In addition, because the frequency of genetic variations can vary by ethnicity,²¹ associations between *COMT* pain vulnerable genotype and pain outcomes were also adjusted for patient ethnicity (European American vs African-American/other). All analyses were conducted using SAS (version 9.2; SAS Institute, Inc, Cary, NC). *P* values <.05 were defined as statistically significant.

RESULTS

Seventy-six patients were screened and determined to be eligible for study participation. Fifty-seven (75%) of these patients consented to study participation. Among these patients, the average number of days between burn injury and burn center admission was 0.6 (0.9) days, and the average number of days between burn center admission and the beginning of the 2-day pain assessment period was 1.4 (0.9) days. Patient characteristics are shown in Table 1. Most patients were young European American men with partial-thickness burn that was ≤10% TBSA. Median family income reported by study participants was \$40,000 to \$60,000.

Table 1. Participant characteristics

	n (%)
N	57
Age (yr), mean ± SD	32 ± 10
Male, n (%)	45 (79)
Ethnicity, n (%)	
European American	39 (68)
African-American	15 (26)
Other	3 (5)
TBSA of burn, n (%)	
1–5%	21 (37)
6–10%	20 (35)
11–15%	11 (19)
16–20%	5 (9)
TBSA of burn that was third degree, n (%)	
0%	34 (60)
1–5%	18 (32)
6–10%	5 (9)
Type of thermal burn, n (%)	
Flame	26 (46)
Grease	13 (23)
Scald	14 (25)
Contact	4 (7)
COMT pain vulnerable genotype, n (%) [*]	
Yes	25 (44)
No	32 (56)

^{*} Defined as COMT genotype that does not contain 1 or more “low pain sensitivity” haplotypes.

During the 2-day study period, 100% (57/57) of participants received opioid analgesics, 11% (6/57) received benzodiazepines, and 2% (1/57) received nonsteroidal anti-inflammatory drugs. Twenty-five (44%) participants had a COMT pain vulnerable genotype. Patients with a COMT pain vulnerable genotype received more opioid and benzodiazepine medications (mean morphine equivalent opioids, 66.5 ± 49.5 vs 53.3 ± 29.7, $P = .247$; mean diazepam equivalent benzodiazepines, 0.6 ± 1.9 vs 0.4 ± 1.8, $P = .804$), although these differences did not reach statistical significance.

Associations between COMT genotype and patient pain experiences are shown in Table 2. Despite receiving more opioid and benzodiazepine medication, individuals with a COMT pain vulnerable genotype had significantly higher “least pain” scores and experienced significantly higher pain on awakening. Overall pain (combination of least, worst, and waking pain scores) was also significantly higher in patients with a COMT pain vulnerable genotype. In contrast, no association was observed between COMT pain vulnerable genotype and worst pain. These associations remained significant when adjusted for total burn size, full-thickness burn size,

Table 2. Association of COMT genotype with pain scores postburn

	COMT Pain Vulnerable Genotype [*]				P
	Yes		No		
	Mean	SE	Mean	SE	
Unadjusted					
Least	4.1	0.3	2.8	0.3	.006
Waking	7.1	0.3	5.6	0.3	.001
Worst	8.8	0.3	8.7	0.3	.790
Overall†	6.7	0.3	5.7	0.2	.011
Adjusted‡					
Least	3.8	0.5	2.6	0.4	.017
Waking	6.8	0.5	5.3	0.4	.004
Worst	8.5	0.5	8.4	0.4	.898
Overall†	6.3	0.4	5.4	0.4	.037

^{*} Defined as COMT genotype that does not contain 1 or more “low pain sensitivity” haplotypes.

† Linear mixed modeling was used to combine six pain measurements (waking, worst, and least pain assessed each day for 2 consecutive days) for each individual into an overall pain score. See Methods section for details.

‡ Adjusted for TBSA, burn depth, age, gender, ethnicity, and time from admission to assessment.

age, gender, ethnicity, and time from admission to study assessment (Table 2).

Associations between selected patient characteristics and overall pain score are shown in Table 3. Age, gender, total burn size, full-thickness burn size, and type of thermal burn had little influence on overall pain severity in our sample. Time from admission to pain assessment was associated with overall pain severity at the trend level. The strength of association between COMT pain vulnerable genotype and overall pain score exceeded that of any other individual or burn characteristics assessed.

DISCUSSION

In our sample, COMT pain vulnerable genotype predicted pain severity upon waking and the least amount of pain that a burn patient experienced during a 24-hour period. In contrast, no association was observed between COMT pain vulnerable genotype and the worst pain that a burn patient experienced during a 24-hour period. This is likely because of a ceiling effect, as ~85% of patients reported a worst pain score ≥7. The presence or absence of a COMT pain vulnerable genotype was a stronger predictor of overall pain severity (combination of least, waking, and worst pain) in the early aftermath of burn injury than the type of thermal burn,

Table 3. Association between selected patient characteristics and overall pain score

	Overall Pain Severity*	
	Mean ± SE	P
Gender		.305
Male	6.0 ± 0.2	
Female	6.5 ± 0.4	
Age (yr)		.878
≤40	6.0 ± 0.2	
>40	6.2 ± 0.4	
Ethnicity		.031
White	6.2 ± 0.2	
Black	6.3 ± 0.4	
Other	4.2 ± 0.8	
Time from admission to study assessment†		.103
≤1 day	6.4 ± 0.3	
>1 day	5.8 ± 0.3	
Thermal burn type		.887
Flame	6.1 ± 0.3	
Other	6.1 ± 0.3	
TBSA burned (%)		.544
0–5	6.3 ± 0.3	
>5	6.0 ± 0.2	
TBSA third degree burned (%)		.254
0	5.9 ± 0.2	
>0%	6.4 ± 0.3	
COMT pain vulnerable genotype‡		.011
Yes	6.7 ± 0.3	
No	5.7 ± 0.2	

* Linear mixed modeling was used to combine six pain measurements (waking, worst, and least pain assessed each day for 2 consecutive days) for each individual into an overall pain score. See Methods section for details.

† Time elapse between admission for burn care and the first day of the 2-day study period.

‡ Defined as *COMT* genotype that does not contain 1 or more “low pain sensitivity” haplotypes.

size or depth of burn, or time from admission to pain assessment. Patients in the sample with more severe pain received more opioid analgesics and more benzodiazepines, indicating that increased pain scores were not the result of reduced pain medication treatment.

Although *COMT* pain vulnerable genotype influenced pain experiences after burn injury, it is important that *COMT* genotype not be viewed as “the genetic determinant” of pain intensity after burn injury. Indeed, the amount of variation in pain associated with the specific risk genotype (genetic variant) assessed in this study is relatively modest. It is also

important to appreciate that the haplotypes used to define the genetic variant in this study are just a few of a number of different genetic factors that may influence the function of the *COMT* enzyme^{22,23} and that the *COMT* enzyme in turn is just one of the great many biologic components of catecholaminergic pathways. The primary utility of this preliminary study is to suggest the potential value using genetic variants influencing components of biological pathways related to catecholamines (and stress systems more broadly) to determine the biologic pathways/mechanisms that most strongly influence postburn pain.

This study identifies a specific link between individual variation in a genetic variant influencing catecholamine metabolism (*COMT* pain vulnerable genotype) and pain after burn injury. In this sample, this genetic variant had more influence on burn pain than burn injury characteristics. This finding is encouraging, as it suggests that novel treatments that target relevant biologic pathways related to stress may have a substantial influence on patient outcomes, even if the characteristics of the burn injury itself are immutable. This is important, because burn-related pain is a major cause of morbidity among burn injury survivors.²⁴

When interpreting our study results, several limitations should be considered. First, our study included only thermal burn patients with TBSA burns ≤20%, and most patients in our sample had burns that were <10% TBSA. However, such burn injuries constitute the majority (>86%) of admissions to major burn centers.²⁵ The generalizability of our findings to patients with larger burns or substantial third-degree burns is unknown. Perhaps more importantly, because patients in this observational study were subsequently to be evaluated for participation in a randomized controlled medication trial, patients with greater than first-degree atrioventricular block; patients taking a β-adrenergic antagonist medication; and patients with asthma, diabetes, coronary artery disease, and congestive heart failure were also excluded. Therefore, the generalizability of study findings to these patient groups cannot be assessed. Also, although our conclusions are valid regarding the relative influence of *COMT* genotype vs burn characteristics on burn-related pain in our sample, our results should not be interpreted as evidence that other burn characteristics do not influence pain. This is because our sample was small and did not include the full range of burn injuries. Finally, as described in the Methods section, we erred when we assumed that patients would be consistently familiar with the term “average.” Because of this, our overall pain score combined waking pain, least pain, and worst pain,

and actual differences regarding the average, or typical, pain experiences of burn patients according to *COMT* genotype are unknown. To prevent this error, future pain studies performed in burn centers should avoid asking patients about their "average pain" (using instead pain "most of the time," etc).

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Case report

Extravasation of contrast material in anterior chest wall: Case report and literature review

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1. Introduction

The use of iodinated contrast material has become the standard for radiographic imaging, but extravasation into subcutaneous tissue is a well-recognized complication that is not without risk. The overwhelming majority of extravasations can be treated conservatively, but rarely severe skin necrosis, brachial plexopathy, or even compartment syndrome will require more invasive treatment. Though the most common extravasation site occurs at the antecubital fossa, this complication can occur at any location.²¹ We present a case of a patient with extravasation of iodinated contrast medium into the right anterior chest wall from a dislodged central venous catheter treated with emergent washout and negative pressure dressing (VACTM).

2. Case report

A 20-year-old male was admitted to the burn intensive care unit after an apartment fire. His injuries involved a total body surface area (TBSA) of 3.5% with partial thickness burns to his fingertips and right flank. He had significant inhalational injury requiring intubation. A right subclavian triple lumen central venous catheter was placed on the day of admission with the catheter tip identified at the superior vena caval/right atrial junction. A computed tomography (CT) scan of the sinuses and chest were ordered revealing pansinusitis and bilateral lung consolidations. The scan also displayed extravasated contrast in the right peri-clavicular soft tissue (Fig. 1).

Approximately 80 mL of Omnipaque-300TM was injected through Medrad EnvisionTM rapid injector via his right subclavian

triple lumen central venous catheter. The extravasated contrast was deep to the pectoralis major muscle and anterior to the clavicle (Fig. 2). No contrast was visualized within the right pleural space or the venous system. The catheter tip, which was in proper position earlier, was noted to be extraluminal in the right subclavian region. A lump was noticed at the right anterior chest wall with no signs of skin discoloration. A right femoral triple lumen central venous catheter was placed emergently. After discussion with radiology and thoracic surgery, the patient was taken to the operating room for right chest exploration, evacuation and irrigation of contrast material and wound VACTM placement.

Post-procedure radiographs revealed dissipation of contrast with no drainable collection. Magnetic resonance imaging (MRI) on post-operative day (POD)#1 revealed no evidence of residual collection in the region and no abnormal enhancement suggesting tissue necrosis. The wound VACTM was changed on POD#2 with minimal inflammation of the surrounding tissue and no signs of tissue necrosis. The remainder of the patients hospital stay was complicated by ventilator dependency requiring tracheostomy, Clostridium difficile colitis, and right main pulmonary artery embolus despite prophylaxis. He was eventually discharged home after 6 weeks without any right anterior chest soft tissue infection, necrosis or brachial plexopathy.

3. Discussion

Subcutaneous extravasation of contrast material is a well-recognized complication occurring in 0.2–0.9% of patients receiving contrast media injection.^{7,8,15,19,21} Frequency of extravasation is higher with mechanical bolus injectors than with hand-injection or drip infusion techniques.^{8,15,19} No correlation has been made between frequency of extravasation with increasing injection rates.^{10,16} No linear correlation is noted between extravasation rates with catheter size, type or location. Yet, in a large series of approximately 70,000 patients, the antecubital fossa was identified as the most frequent site of extravasation (44.8%). The shoulder was the site of extravasation in five adults (1.1%) and one pediatric patient.²¹

Those who are unable to communicate or respond to pain, such as infants or sedated patients, are more likely to develop extravasation injuries. Patients receiving chemotherapy have increased fragility of vein walls and increased risk of extravasation. Extravasation injury can be more severe in patients with arterial

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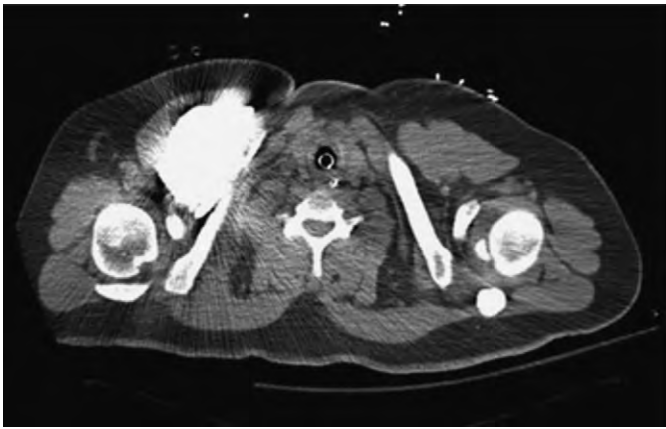


Fig. 1. Thoracic CT scan demonstrating contrast in the right peri-clavicular space measuring $5.9 \times 10.6 \times 11.2$ centimeters (cm).

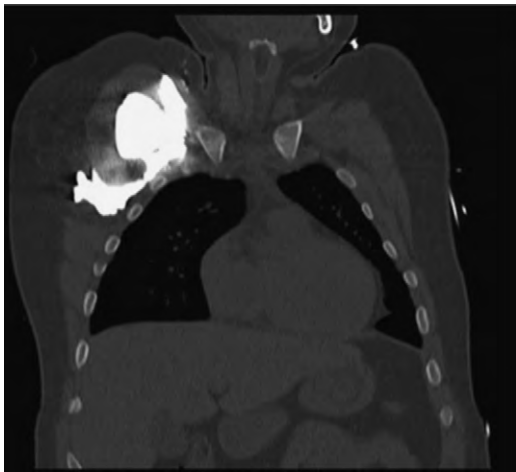


Fig. 2. Coronal thoracic CT scan identifying IV contrast anterior to the clavicle and deep to the pectoralis major muscle. Notice the lack of contrast within the right pleural space or the venous system.

insufficiency, venous thrombosis, or lymphatic drainage compromise due to loss of normal circulatory function.²

The vast majority of extravasations involve small amounts, which heal quickly.^{4,8,19} Severe damage is usually a consequence of larger volumes (>50 mL) and commonly involved mechanical injectors.^{2,15} Rarely, small amounts (10 mL) can cause skin necrosis and ulceration.¹

The osmolality and cytotoxicity of contrast media is significant. Low-osmolar contrast media better tolerated than high osmolar media. (The threshold for injury is ~ 1.025 – 1.420 mOsm/kg water.)¹⁹ High osmolar media is associated with increased incidence of necrosis, bleeding, and oedema evidenced in rat extravasation studies.⁶ Studies have also shown that ionic contrast media is more toxic, causing an acute, then chronic inflammatory reaction with fibrosis and adjacent muscle atrophy detected at 8 weeks. This reaction peaks at 24–48 h after extravasation.^{5,13}

The clinical presentation of extravasation is quite variable. Injury can range from minimal erythema and oedema to frank tissue necrosis and skin ulceration. Though rare, weakness, pain, and hypoesthesia have been reported as long term sequelae when not treated within an appropriate timeframe.⁸ Compartment syndrome has been documented in several cases presenting as tense, dusky forearms with diminished pulses that require emergent fasciotomy.^{2,3,17,21} Wang et al reported a brachial

plexopathy in a pediatric patient with extravasation into the axilla from an indwelling venous catheter.²¹

Most patients complain of a stinging or burning sensation, while some may have no symptoms at all. The site of extravasation will usually be tender with a red and swollen appearance. The majority of injuries will resolve spontaneously within 2–4 days, but this is difficult to predict based on initial exam.² Severely injured tissue will have skin blistering, altered tissue perfusion, paresthesia and increasing or persistent pain after 4 h.⁴

Local irritative or hypersensitivity reactions to contrast agents can be confused as extravasation injuries. Localized transient pain and delayed pain has been noted in up to 5% and 14%, respectively, in patients following intravenous administration of contrast material. Evaluation of the region will reveal the area to be tender, but without swelling or erythema. The catheter will also be appropriately situated within the vein.^{14,18}

Extravasation of contrast can occur by several methods, but most commonly from dislodgement of catheters from their intravenous locations. As in our patient, the central venous catheter was accidentally dislodged during transfer despite being secured to the skin. Proper methods of securing venous access is imperative in preventing extravasation, as well as attention to detail and care when transferring patients.

Several approaches of treatment exist for extravasation injuries, without a consensus for the best management. The approaches can be classified as either conservative or surgical. Most extravasation injuries will heal without surgery and therefore conservative therapy is often recommended. The affected limb should be elevated. Topical application of heat will cause vasodilatation, absorbing the contrast material. Cold application will produce vasoconstriction, limiting inflammation.⁹

Local subcutaneous injections of hyaluronidase have been recommended for patients with large volume extravasations. Hyaluronidase breaks down connective tissue and facilitates the absorption of the extravasated material.¹¹ It is well tolerated and often used for chemotherapeutic agent extravasations. Evidence for the treatment of contrast material is anecdotal with conflicting reports.^{4,8,13}

Emergent suction is safe and effective in preventing severe effects of extravasation injuries. Loth and Jones recommended prompt surgical drainage and suction of extravasated contrast medium for any volume greater than 20 mL within 6 h.¹² Vandeweyer performed emergent liposuction with saline washout within 2 h for 11 patients with forearm extravasation injuries, noting complete healing in all patients.²⁰ The use of negative pressure dressings, including VACTM, for extravasation injuries is a new and useful tool.

Few studies have focused on extravasation of contrast material into the anterior chest wall. Wang et al noted a brachial plexopathy in a patient with a minimal amount of contrast extravasation into the axilla or anterior chest wall.²¹ Due to the inability to conservatively treat extravasation in this region, we recommend early surgical drainage and saline washout in order to prevent long term damage. Still, the majority of injuries from extravasated contrast can be treated conservatively, with early surgical treatment for large volume extravasations.

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Evaluation of Burn Center Patients with Hemoglobin Concentrations Below 7.0 g/dL

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Introduction In 1995, Corwin et al reported the lack of a clear indication for up to 29% of ICU transfusions.¹ Recently, transfusion of elderly non-cardiac surgery patients was associated with a higher 30 day mortality.² Several studies have questioned the current transfusion trigger thresholds and routine transfusion of patients.³⁻⁵ Transfusion practices in thermally injured patients and the potential for increased risk for mortality has been recently questioned.⁶ This retrospective analysis evaluates our transfusion practice and impact of transfusions in burn patients.

Materials and Methods Following IRB approval, Hemoglobin (HGB) data from January 1, 2000 to December 31, 2011 were reviewed and demonstrated 258 patients with HGB levels < 7 g/dL among 3771 burn center admissions. Patient data included: ethanol and tobacco exposure, history of hypertension, diabetes, inhalation injury (INH), heart failure, and myocardial infarction (MI). Patient age, height, weight, involved body surface area (TBSA), length of stay (LOS), modified Baux score, surgical history, transfusions (TXF), heart rate >110 bpm (TACHY) during low HGB, need for vasopressors (VP), ventilator support (VENT), temperature increase over 2° F within 24 h (HIGH T) or chest x-ray changes following TXF, and fluid status (I&O) prior to HGB < 7 g/dL were also collected. Survivor status (SURV), days of HGB < 7, INH, and MI were studied. TXF at 1-2 days, 3 to 5 days, 6 to 7 days and more than 2 weeks with a HGB < 7 g/dL were collected. A post-HOC paired analysis of survivors matched for INH, age, and %TBSA was done to clarify any apparent negative impact of blood transfusion.

Results

Demographic data for all patients with HGB < 7 g/dL are provided in Table 1. Distribution of %TBSA for SURV stratified by TXF status is provided in figure 1. HGB < 7.0 for 24 h was noted in 6.8% of 3771 admissions. HGB remained below 7 g for 24 h in 86 (33%) patients while for the remaining patients, the median days with HGB < 7 was 5 days (25%-75% IQR 3 and 8 days). 43 of 258 patients (17%) had HGB < 7 g/dL for more than 8 days. INH was noted in 155 of 258 patients (60%) requiring VENT for a median of 25 days (see Table 1). Surgical interventions were required for 199 of 258 patients (77%). Median fluid excess at the time of HGB < 7 g/dL was 1204 mL (IQR range -1493 to 3477 mL). Linear regression ($y = 1.1688x + 559.53$, $r^2 < 0.05$) was not instructive in explaining HGB < 7 g/dL. TXF-associated HIGH T occurred 89 times in 77 patients (29.8%).

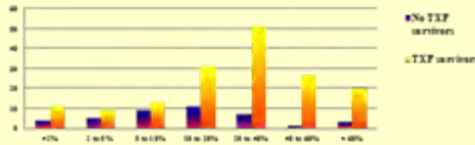
INH Patients. VP use was more common with INH (< 0.05) and INH patients received more TXF ($T = 1.809$; $p < 0.05$). INH patients were younger ($T = 2.055$; $p < 0.05$), had larger TBSA ($T = 3.018$; $p < 0.05$), were smokers, and had positive ETOH level. Diabetics, heart failure, or MI were less common among INH.

Table 1. All Patients with a Hemoglobin < 7 g/dL from 2000 to 2011

	Age	TBSA (%)	Lowest hgb	LOS (days)	Vent Days	% with INH
All Patients = 258	47 (35 - 62)	23 (10 - 41.5)	6.2 (5.8 - 6.6)	40 (24 - 61)	25 (14 - 42)	57.8%
Patients not transfused = 49	47 (39 - 61)	12 (5.5 - 26.5)	6.5 (6.2 - 6.9)	26 (17 - 39)	14.5 (10 - 20)	49%
p	NS*	<0.05*	<0.05*	<0.05*	<0.05*	NS*
Patients transfused = 209	47 (35 - 63)	27 (11 - 42)	6.1 (5.7 - 6.6)	45 (27 - 69)	27 (16 - 45)	62.7%

@ students' T-Test

Figure 1. Distribution of Burn Size for Transfused and Non-transfused Survivors with HGB < 7



TXF and Non-TXF Patients. The average number of TXF was 10.5 \pm 11.6 (median 6; IQR 2 to 14) units/patient. Low HGB resolved in 49 patients (17%) without TXF. Percent TBSA was significant and older patients received earlier TXF ($T = 2.683$; $p < 0.05$). This was less marked with SURV only patients ($T = 1.83$; $p < 0.05$). No difference in VENT days was noted with early TXF for all patients and for SURV-only analysis (Confer Table 1 and Table 2). More women received TXF within 24 hours of HGB < 7 g/dL. TXF within the first 24 hours was not due to INH, nor did MI history differ when compared to later TXF and no TXF patients. Stratification by SURV demonstrated that only MI history differed. **Early vs. Late TXF.** Early TXF within 24 hours of a low HGB correlated only with patient age. Patients with > 24 h delayed or no TXF had a shorter LOS ($T = 3.64$; $p < 0.05$), however, comparison using only SURV was less marked ($T = 2.074$; $p < 0.05$). Further analysis of the delay in TXF demonstrated increased mortality in patients receiving TXF within 2 days versus the remaining time periods ($\chi^2 = 1.596$; $P < 0.05$). Fewer of these early TXF patients were grafted, and more required VP. TXF status did not differ for gender, and did not relate to underlying diseases except for MI where TXF was more common ($\chi^2 = 0.003$; $p < 0.05$). Stratification by days with low hemoglobin ANOVA demonstrated a shorter LOS attributable to early mortality ($F = 6.012$; $P < 0.05$) and no difference in VENT ($F = 0.403$; $p > 0.05$). Patients receiving TXF within 48 hours of HGB < 7.0 g/dL were older ($F = 5.205$; $p < 0.05$) but were not different in TBSA with the other TXF groups ($F = 1.028$; $p > 0.05$).

NON-SURV analysis. TXF and non-TXF non-SURV did not differ in LOS ($T = 0.569$; $p > 0.05$); in Baux score, age, TBSA, VENT, or low HGB. TACHY was greater in non-TXF non-SURV ($T = 3.368$; $p < 0.05$).

Table 2. Demographics of Surviving Patients with HGB < 7 g/dL

	Age	TBSA (%)	Lowest HGB	LOS (days)	Vent Days	% with INH
All Survivors	47 (35-63)	27 (11-42)	6.1 (5.7-6.6)	45 (27-69)	27 (16-45)	59.4%
Patients not transfused	46.5 (38.5-57)	12 (5.5-26.5)	6.5 (6.2-6.9)	27.5 (18.5-39)	14.5 (11-20)	45%
p	NS*	<0.05*	<0.05*	<0.05*	<0.05*	NS*
Patients transfused	47 (34-61)	25.9 (11.3-41.5)	6.1 (5.7-6.6)	41 (31-77)	29.5 (17-48)	63%

@ students' T-Test

Results (continued)

Cardiac Disease. MI/heart failure was noted in 53 patients (20.5%). MI history was reported in 45 of these patients. Comparison of lowest HGB with other groups was not significantly different ($p > 0.05$). All but 5 of these 45 patients were given TXF in the first 24 hours after a HGB < 7.0 g/dL (10%). TACHY, viewed as stress from a HGB < 7 was possibly resolved by TXF in only 18 of 40 TXF MI patients (45%). Mortality in those with a history of MI was 15 (33%) and was independent of gender, INH, grafting, vasopressor use, or TXF. Baux scores, and LOS did not differ nor did lowest HGB concentration or days with < 7 g/dL HGB or days with TACHY. With our sample size it appears that TXF does not impact survival in patients with history of MI.

Paired analysis. Non-TXF patients (N=40) were paired with TXF patient (N=40) with a comparable age, TBSA, and INH. Survival, gender, INH, surgery, ethanol or tobacco use, hypertension, and diabetes were not statistically different. TXF patients had lower HGB, more chest x-ray changes ($p = 0.03$), but fewer required VP ($p = 0.03$). Paired t-test noted a longer LOS for TXF patients ($T = 4.499$; $p < 0.05$) and prolonged VENT ($T = 2.57$; $p < 0.05$).

Table 3. Median and IRQ for 40 Patient Paired Analysis

	Age (years)	TBSA (%)	Lowest HGB	LOS (days)	Vent Days	% w/in intubation
Patients not transfused = 40	47 (39 - 61)	12 (5.5 - 26.5)	6.5 (6.2 - 6.9)	26 (17 - 39)	14.5 (10.3 - 20)	60%
p	NS**	NS**	<0.05**	<0.05**	<0.05**	NS*
Patients transfused = 40	50 (42 - 61)	12.5 (8 - 30)	5.9 (5.7 - 6.3)	48 (30 - 61)	27 (16 - 40)	57.5%

@ students' paired t-test comparison; *expected NS for paired groups; **Chi-square comparison

Discussion

TXF triggers in burn admissions vary considerably among burn treatment centers. The rationale for TXF is that tachycardia and cardiac stressors will be improved by keeping HGB > 10 g/dL, and is often recommended by cardiology and other consultants. The observed longer LOS, VENT, and TACHY in TXF patients were confirmed by the paired analysis. The HIGH T and chest x-ray changes among TXF patients are also of concern. Patients in two studies with a lower TXF trigger (7g/dL) demonstrated lower mortality when compared to more liberal TXF triggers around 10 g/dL.^{3,4}

Conclusion

For all groups TXF increased morbidity, prolonged LOS, and did not decrease mortality in patients with history of MI bringing to question current TXF practices. TXF in the patients with a history of MI group was inadequately sized for statistical significance. For history of MI patients survival was not different with use of TXF vs. non TXF (60% vs 67%). The paired analysis of 40 TXF and 40 non-TXF patients confirmed our finds of longer LOS and VENT for TXF patients. Survival for all groups with 78%

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ABSTRACT

INTRODUCTION: Drug-induced adverse effects are unexpected findings with the use of oral and intravenous antimicrobial agents. In addition to exfoliative rashes, trimethoprim causes sudden and profound HK in 10 to 20% of patients treated with this drug. Pharmacokinetic and drug metabolism changes associated with thermal injury as well as physiologic changes may impact this drug effect.

MATERIALS AND METHODS: Following IRB approval for a retrospective study, 224 patients were identified who had been treated with trimethoprim sulfamethoxazole (T/S). The manufacturer recommends dose adjustment at ≤ 30 ml/min. To assure no underlying renal impairment cause for HK, 24 patients were excluded because they had creatinine clearances < 50 mL/min. leaving 200 patients for analysis. Three definitions of Drug-induced HK were used: 1) a 1 mEq/L or more rise, 2) a rise warranting early discontinuation of T/S and 3) “marked” HK as serum potassium of 5.5 mEq/L or higher. A potassium level prior to T/S treatment (PreK) and a level during T/S therapy (TxK) were collected. Initial analysis of demographic data were age, creatinine clearance (CLCR), total body surface area burn (TBSA), ISS, burn probability of survival score (burn P), alternate probability of survival score (A burn p), ventilator days, length of stay (LOS), mg/kg of trimethoprim (D TMP) and survival. Pairwise data were analyzed with students t-test and categorical data using X^2 seeking significance at 0.05.

RESULTS: Between 2005 and 2010, 200 patients were exposed to trimethoprim for which 31 patients (15.5%) had elevation of potassium (1st definition), two additional patients required discontinuation (2nd definition) and 13 (6.5%) had marked hyperkalemia (> 5.5 mEq/L) that resolved with discontinuation of the drug. For 166 patients (82%) HK was not observed (PreK 3.9 ± 0.4 and TxK 4.3 ± 0.5 mEq/L. For 34 patients (15.5%) HK was observed (1st definition) with Pre K 4.0 ± 0.5 and TxK 5.3 ± 0.7 mEq/L. Survival for no HK patients was 97% and 94% for HK patients. Gender did not differ between groups. For 12 risk factors for HK in the literature, only the number with a history of hypertension and need for intubation was significantly different for the HK patients. T-test comparison of initial analysis parameters was not statistically significant except for TBSA, LOS and D TMP ($P < 0.05$) (see below). Patients less than 30 years of age were 25.9% (43 of 166) 26% (9 of 34) for the Non-HK and HK patients, respectively. CLCR was < 60 ml/min was 17% (28 of 166) versus none for the non HK and HK patients, respectively. TBSA $> 20\%$ was 15% (25 of 166) and 35% (12 of 34) for the non HK and HK patients respectively.

DISCUSSION: A nearly 20% incidence of HK in burn patients and serious HK in 6% is consistent with the literature in non-burn patients. These data would suggest early initiation of oral T/S and routine serum potassium monitoring prior to discharge and careful monitoring of patients requiring IV or PO T/S for pulmonary infections.

INTRODUCTION

Oral antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA) are limited to clindamycin, linezolid, and trimethoprim-sulfamethoxazole (T/S). Oral linezolid remains a costly treatment for patients and clindamycin and T/S have a high incidence of drug rash. In addition, the trimethoprim (TMP) component of T/S can cause sudden hyperkalemia (HK).^{1,2} This T/S adverse reaction is not uncommon in burn patients, having been observed prior to patient discharge. Drug-induced HK is defined as either a serum potassium (K) ≥ 5.0 or a 1 mEq rise in serum K.³ Because patients are often converted to oral antibiotics just prior to discharge, HK may not be noted until the patient returns to clinic.⁴ HK is associated with arrhythmias, hypotension, ileus, and areflexia. The purpose of this quality assurance investigation is to determine the incidence of HK among patients treated with T/S. Using retrospective data collection, the investigators hope to determine if underlying diseases, medication exposures, or other documented findings show any correlation with the onset of this adverse effect. The investigators determined how commonly HK occurs and have studied the affected patients for any predisposing factors.

METHODS AND MATERIALS

Following IRB approval, a retrospective study of 224 patients treated with oral or intravenous T/S was begun using pharmacy data. Patients (n = 201) with calculated creatinine clearance (CLCR) ≥ 50 ml/min were evaluated for HK with T/S treatment. Patient history of ETOH, tobacco, illicit drug use, underlying disease, and other drug exposures were analyzed using X^2 . Prior serum K, K with T/S treatment, age, CLCR, %TBSA, ventilator days, and mg/kg/day TMP daily dose were analyzed by students’ t-test and with non-normal distributions, mean difference seeking an p value of ≤ 0.05 . Demographic data are provided in **Table 1** below.

Table 1. Patients stratified by non-renal impairment- induced hyperkalemia following TMP

	Age (years)	CLCR (mL/min)	%TBSA	LOS (days)	TMP (mg/kg/day)
Patients with Trimethoprim-induced Hyperkalemia					
MEAN	44.6	106.3	18.9	41.6	6.2
±Std Dev	±20.6	±40.9	±21.7	±42.0	±3.7
Patients with No Change in Serum Potassium following Trimethoprim Exposure					
MEAN	42.0	107.2	11.7	20.0	7.5
±Std Dev	±17.0	±5.2	±14.7	±26.9	±1.9
T or Z value	T=1.011	Z=0.196	Z=1.097	Z=3.010	Z=2.050
P value	NS	NS	NS	<0.05	<0.05

RESULTS

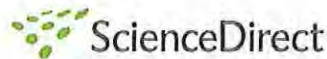
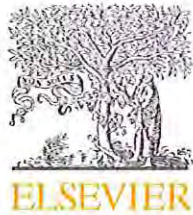
Recommended TMP/SMX doses for skin infection are 10 mg/kg per day, however, our study used ± 2.4 mg/kg/day. In spite of this lower average dose, 36 of 201 (18%) experienced HK with T/S. Prior serum K and age did not differ between these groups. No patient with normal serum K had HK but 7 of 36 (19%) with HK did. Ethanol, tobacco, and drug abuse did not differ between groups ($p >> 0.05$). Heparin exposure (non-ambulatory patients) diuretic use, use of ACE inhibitors did not differ between groups ($X^2 = < 1.0$; $p >> 0.05$).

CONCLUSIONS

HK due to TMP results from the drug binding to membrane-bound ion transport proteins independent or due to differences in drug disposition. CLCR and TMP dose > 8 mg/kg/day were distributed in both groups. Diseases like heart failure and hypertension did not impact HK. Occult nephropathy of AIDS may predispose patients to HK as 7 HK patients had AIDS and 1 normal serum K had AIDS. The incidence of HK among burn patients was 20% and among non-burn patient populations treated with T/S. This finding, combined with the review of underlying diseases and burn size did not provide clear risk factors for HK. TMP mg/kg/day was significantly higher in HK but data were not normally distributed. These findings may suggest that some unknown mechanism of expression providing additional peptides for TMP binding occurs consistently in HK patients who have a burn injury.

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Case report

Infiltration of sodium valproate with compartment syndrome and bullous reaction: Case report and literature review

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1. Introduction

Intravenous sodium valproate therapy has been used to treat epileptic and post-traumatic seizures, as well as bipolar disorder, since 1996 [1]. For patients with a seizure history or a mood disorder requiring treatment, missed doses due to n.p.o. status preceding surgery often results in administration of intravenous doses. Intravenous administration of valproate is usually relegated to emergency seizures, and it has been shown to cause adverse reactions in patients requiring parenteral doses including transient injection site irritation [2]. There are no clear guidelines concerning intravenous administration of sodium valproate. We present the case of a patient with infiltration of intravenous sodium valproate during infusion into a hand vein site with resulting extravasation, a bullous skin reaction, and progression to compartment syndrome of the right upper extremity.

2. Case presentation

A 62-year-old male was admitted to the emergency department of his local hospital with chief complaints of abdominal

pain, distention, hematemesis and fever of 103.3 °F. His past medical history is significant for mood disorder treated with valproic acid, developmental disability, dementia, transient ischemic attack (TIA), left cerebellar/parietal encephalomalacia, diverticulosis, gastroesophageal reflux disease (GERD), and peptic ulcer disease (PUD). Screening laboratory tests were obtained and were unremarkable with the exception of a lactic acid level of 6.4 mmol/L. Blood cultures and chest X-ray results were unremarkable. Abdominal X-ray revealed a non-obstructive pattern with a few air fluid levels. As part of the evaluation of abdominal symptoms, an abdominal pelvic CT scan was obtained, which showed marked gastric distention. The patient was kept n.p.o. and placed on intravenous fluids in anticipation of the need for surgical management for his abdominal pain. The patient was transferred to Crozer Chester Medical Center for management of his abdominal pain by a general surgical team.

The patient's current condition was assessed, his past medical history was reviewed, and the various neurological disorders were taken into consideration. The patient was adequately resuscitated, was kept n.p.o. and on intravenous hydration. He was started on broad spectrum antibiotics for suspected sepsis. Gastric distention was decompressed by placement of nasogastric tube and serial abdominal examinations were conducted. Patient was adequately responding to the treatment, reflected by resolution of abdominal pain, lactic acidosis and stable hemoglobin.

Management of adult patients with developmental delay and dementia often requires use of neuroleptics and antic-

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Fig. 1 – PA view of right upper extremity with elbow at 90° immediately after extravasation of valproate sodium demonstrating bullae without subcutaneous air.

onvulsants in combination to manage behavior. The patient was chronically treated with sodium valproate prior to this admission. It was decided to administer sodium valproate parenterally at a dose equivalent to the oral dose in order to maintain mood stabilization. As a result, an infusion of 500 mg sodium valproate was prescribed for the patient every 12 h until the patient would be able to receive his regularly scheduled oral doses.

The first parenteral dose of valproic acid (500 mg in 50 mL of 5% dextrose in water) was delivered through a peripheral line that had been placed into a hand vein by the transferring hospital. The infusion was administered using an infusion pump with an expected duration of infusion of approximately 30 min. Immediately following the initiation of the valproate infusion, his right upper extremity became edematous with

the appearance of erythema extending from his wrist and progressing rapidly toward the arm. The infusion was discontinued, but the patient now demonstrated an appearance of large fluid-filled bullae extending from the hand, across the dorsal surface of the forearm to the elbow. The edema and blistering continued to progress over the course of the next 20 min. An X-ray of the right upper extremity obtained soon after the extravasation displayed marked edema and the shadows of bullae on the forearm without any evidence of subcutaneous air (see Fig. 1). The edema and the extravasated fluid progressed to compartment syndrome in the patient's right upper extremity. This was clinically recognized by the team. Assessment of the compartment syndrome was accomplished with tissue pressure measurement using an arterial system method. An 18-gauge needle was inserted to a well-prepared and anesthetized forearm. This catheter was then attached to the conventional closed arterial system. The transducer cable was attached to the pressure monitor. The placement of the needle in the appropriate compartments were confirmed by the pressure increase noted on the monitor. Tissue pressures were obtained in the volar and dorsal aspect of the forearm and measured 44 mmHg. These resulting pressures warranted escharotomy (Fig. 2).

The bullae were drained of approximately 300 mL of accumulated tissue fluid, and the fluid was cultured as part of routine intraoperative procedure. This later showed negative growth of any bacteria, yeast, or other organism.



Fig. 2 – AP view of ventral surface of right upper extremity immediately after extravasation of valproate sodium demonstrating bullae without subcutaneous air.

Medial and lateral escharotomies were made extending from the wrist to the mid arm. Adequate relief of the accumulated tissue pressure was confirmed by a postoperative tissue pressure measured 10 mmHg in an extended arm in the operating room. In the operating room, both the debridement of the bullous lesions and the escharotomies were performed without complication. Post-operative care of the patient following escharotomy was assumed by the Nathan Speare Regional Burn Treatment Center.

On the postoperative day 9, the patient was taken to the operating room for closure of the escharotomy wounds. This was achieved primarily with approximation of the skin edges using surgical staples. Over the next week, the wound was evaluated daily for healing and re-epithelialization of the areas where the debridement of bullae had been carried out. He was discharged from the burn treatment center 11 days after the onset of the skin reaction and was discharged from the hospital.

3. Discussion

Compartment syndrome requires urgent care by a surgical team. It is commonly caused by traumatic injury to blood vessels or bone, ischemic reperfusion injury, excessive exercise, circumferential and non-circumferential thermal injury, and prolonged tissue compression during surgical procedures [3]. It occurs most frequently in the leg and forearm, but has also been observed in the arm, foot, hand, buttock, and is increasingly reported in the abdominal cavity following trauma and burns [3]. Patients with compartment syndrome of the extremities most frequently present with acute onset of pain, restricted mobility of the affected limb, and swelling [4].

Escharotomy or fasciotomy is recommended to alleviate pressure when absolute intracompartmental pressure is above 30 mmHg. At this point, capillary pressure is not large enough to maintain blood flow and ischemic nerve dysfunction can occur when this elevated tissue pressure is maintained in excess of 6 h [3]. Complications following compartment syndrome also include nerve damage, vascular damage, hematoma, DVT, and infection [5,6]; however, an overwhelming majority of patients will have a full return of limb function as a result of escharotomy or fasciotomy.

A handful of cases of compartment syndrome of the forearm and hand have been reportedly caused by extravasation of intravenously-delivered materials [7–10]. The properties of the medication involved and osmolarity of the infused solution appear to result in the formation of “non-allergic” response bullae [8,10]. The pK_a of valproic acid is 4.8 and sodium valproate is pH-adjusted to 7.6 using hydrochloric acid in intravenous solutions [11]. This would indicate that valproate would be approximately 50% ionized intracellularly. Valproic acid distribution into the cell and into the cell membrane is driven by the pH gradient between the intracellular pH of the ischemic tissue and that of the blood. The impact of locally accumulated valproic acid in skin cell membranes is unknown, but is certain to have resulted directly or indirectly in the flaccid bullae that rapidly presented on this patient's arm and the resulting compartment syndrome.

Intravenous valproate therapy is frequently used when oral administration is contraindicated in acute situations and when the enteral route of drug administration cannot be used safely. Parenteral sodium valproate has been shown in randomized clinical trials to be well-tolerated in loading doses of up to 30 mg/kg and with infusion rates up to 10 mg/kg/min. These publications have demonstrated no significant change in a patient's heart rate or mean arterial pressure during the infusion, nor the appearance of rash or other than expected infusion-related pain. These publications, though, do demonstrate that 81.5% of patients experience short-lived pain and burning or paresthesia at the injection site used for parenteral administration of sodium valproate [1]. Prolonged pain and inflammation at the injection site occur in up to 2.6% of patients [11]. For patients with a prolonged history of valproate use, the appearance of bullous lesions is unlikely to represent a sudden dermatotoxic reaction to the medication [12]. Valproate's prolonged toxic effects are believed to be caused by several of its long half-life metabolites [13].

In extremely rare cases, use of valproic acid has been shown to change hair color and structure [3], and can also affect nail and skin growth [14]. With high concentrations of valproate, it may be that local toxicity to other skin structures might cause the formation of the impressive bullae seen in this case. Given that desmosomes function to hold the epidermis to the dermis, such local toxicity may result from accumulation of valproate into these structures resulting in dysfunction. Although this is speculative, it warrants consideration for the rapid onset of bullae.

In vitro studies have demonstrated that valproic acid does dissolve in the cell membranes at high concentrations and thus acts in a receptor-independent manner, perhaps to exert some of its reported toxicity. Valproate has been demonstrated to partition the mammalian cell lipid bilayers by dissolving into the phosphorylated fatty acid layers [15]. This behavior may or may not contribute to its well-known anticonvulsant effects [16]. The lipid solubility of its unionized organic acid form (valproic acid) certainly would allow large numbers of molecules to diffuse across the cell membranes.

Among the metabolic findings induced by valproate exposure is the observation that carnitine has been shown to reverse valproate toxicity in pediatric cases. This finding has been attributed to the formation of valproate and carnitine into valproylcarnitine ester by mitochondrial carnitine acyltransferases. This production of valproylcarnitine has been implicated as the cause of serum carnitine deficiencies associated with long-term valproate therapy [13,17]. Depletion of tissue carnitine might also contribute to the observed dermatotoxicity only associated with this single infusion and not noted with restoration of oral therapy [18]. This patient received long-term valproate for a number of years, and thus depletion of his tissue carnitine levels may have contributed to the rapid dermatotoxicity noted during the infusion.

Few case reports have reported compartment syndrome resulting from extravasation of parenterally administered medications, but none following extravasation of sodium valproate. Even with the manufacturer's recommended infusion rate, compartment syndrome and dermatotoxicity occurred. On reflection, perhaps central venous administration should have been used for the infusion rather than a hand

vein. The use of valproate infusion into a hand vein, a site often associated with venous trauma and extravasation risk, should be avoided. With extravasation of valproate and the development of a compartment syndrome of the infused limb, escharotomy was necessary to decrease tissue pressure and restore blood flow to the affected extremity.

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An Open, Prospective, Randomized Pilot Investigation Evaluating Pain With the Use of a Soft Silicone Wound Contact Layer Vs Bridal Veil and Staples on Split Thickness Skin Grafts as a Primary Dressing

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An open, prospective, randomized, pilot investigation was implemented to evaluate the pain, cost-effectiveness, ease of use, tolerance, efficacy, and safety of a soft silicone wound contact layer (Mepitel® One) vs Bridal Veil and staples used on split thickness skin grafts in the treatment of deep partial or full-thickness thermal burns. Individuals aged between 18 and 70 years with deep partial or full-thickness thermal burns (1–25% TBSA) were randomized into two groups and treated for 14 days or until greater than 95% graft take was achieved, whichever occurred first. Data were obtained and analyzed on pain experienced before, during, and after dressing removal. Secondary considerations included the overall cost (direct), graft take and healing, the ease of product use, overall experience of the dressing, and adverse events. A total of 43 subjects were recruited. There were no significant differences in burn area profiles within the groups. The pain level during dressing removal was significant between the groups ($P = .0118$) with the removal of Mepitel One being less painful. The staff costs were lower in the group of patients treated with Mepitel One ($P = .0064$) as reflected in the shorter time required for dressing removal ($P = .0005$), with Mepitel One taking on average less than a quarter of the time to remove. There was no significant difference in healing between the two groups, with 99.0% of the Mepitel One group and 93.1% of the Bridal Veil and staples group showing greater than 95% graft take at post-op day 7 (+/-1) ($P = .2373$). Clinicians reported that the soft silicone dressing was easier to use, more conformable, and demonstrated better ability to stay in place, compared with the Bridal Veil and staples regime. Both treatments were well tolerated, with no serious adverse events in either treatment group. Mepitel One was at least as effective in the treatment of patients as the standard care (Bridal Veil and staples). In addition, the group of patients treated with the soft silicone dressing demonstrated decreased pain and lower costs associated with treatment. (J Burn Care Res 2013;34:XXX–XXX)

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Burns are, unfortunately, a common injury with as many as 450,000 people in the United States suffering burns that require treatment.¹ Burn treatment depends on the type of injury. Superficial burns can often be easily treated, usually with a conservative approach by topical medication, or with some type of dressing or covering that promotes the natural course of healing. For deep dermal burns, a combination of excision and grafting is preferred.² Areas of burn injury that initially appear more superficial can sometimes become deeper over a period of 48 to 72 hours, resulting in necrosis of the burn wound from

infection or poor perfusion to the affected area.³ This resulting conversion to a deeper burn then requires excision and grafting.

Skin grafts are placed over excised areas of full thickness injuries and are usually attached with sutures or staples.³ Staples are often the preferred method of attachment because sutures take more time to close the wound and require a higher level of skill.⁴ Although staples are useful in anchoring grafts in place, subjects often complain that they cause pain as wound healing progresses. The use of staples can also increase the risk of infection and scarring.^{5,6} Pulling and sticking are common complaints, and there is the possibility that staples can become embedded in the graft. This leads to disruption of an otherwise healed area, increased pain, and anxiety for the subject as well as anxiety for the staff. When dressing changes require staple removal, patients experience varying degrees of pain and anxiety. Anxiety during dressing changes can sometimes be mistaken for pain, resulting in the potential for oversedation, which is detrimental to the subject.⁷ Unfortunately, the pain is often mismanaged and subjects suffer more pain than is necessary.⁸ Furthermore, wound-related pain can cause psychological stress which may, in turn, delay healing.⁹ Thus, there remains a need for less painful methods of fixing grafts to the wound bed. Pain is subjective and anxiety often confounds a true pain assessment in subjects who are alert. The visual analog pain scoring system is a reliable method for measuring pain in burn subjects and was used in this study.¹⁰⁻¹²

Other methods of fixing skin grafts such as fibrin sealants are in use¹³ and these alleviate the need for staples; however, successful use is dependent on appropriate technique. In some circumstances, the sealants can fail to adhere;¹⁴ this is a particular problem with moist conditions. If fibrin sealants are applied too thickly, wound healing is slowed down.¹⁵

Graft take can be optimized with appropriate medical management. The use of non-adherent dressings to protect the graft is customary. Various types of netting-style dressings are used by many burn clinicians. One such type is Bridal Veil, which is a commercially available, sterile product that comes in 2.0-, 3.0-, and 4.0-mm hexagonal mesh sizes. Grafts are fixated with staples under and sometimes over the Bridal Veil to secure them in place. For the purposes of this study, the term Bridal Veil is used generically. Three study sites used Conformant 2[®] Wound Veil (Smith and Nephew, Hull) and one site used commercially available Bridal Veil.

Silicone net dressings have also been used successfully to prevent the lifting and adherence of skin grafts to dressings, minimize pain, and promote healing.¹⁶⁻²⁰ Soft silicone dressings have been used in many areas of wound healing, for example, in the treatment of noncomplex burns.²¹⁻²³ They have also been used successfully to retain secure skin tears in situ.^{24,25} Mepitel[®] One (Molnlycke Health Care, Gothenburg) is a sterile, transparent, and flexible wound contact layer consisting of perforated polyurethane film coated with Safetac[®] soft silicone adhesive on one side. Mepitel One is available in various sizes and can be left in place for several days (up to 14 days) depending on the wound/skin condition.²⁶ This product firmly fixes to clean, intact peripheral skin, thus eliminating the need for staples.

Appropriate secondary dressings can also enhance graft take. Bolster-style dressings that provide adequate absorbency are acceptable. These dressings are also designed to apply mild pressure to the wound in order to promote uniform adherence of the graft to the wound bed, and to prevent shear forces from shifting the graft on the wound bed.³ The secondary dressings can be changed as required without removing the primary dressing as long as the primary dressing allows the passage of exudate.

An open, prospective, randomized, pilot investigation was implemented to evaluate the use of Mepitel One vs Bridal Veil and staples on deep partial or full thickness burns requiring skin grafts. The primary objective of this Institutional Review Board-approved study was to compare pain at the time of dressing removal for the two treatments. The secondary objectives were to compare the two treatments in terms of overall costs, ease of use, adherence, tolerance, safety, and efficacy.

METHODS

Patient Selection

A total of 43 patients (aged between 18 and 70 years and of both genders) who presented with 1 to 25% TBSA deep partial or full-thickness burns requiring skin grafting met all the inclusion/exclusion criteria of the study (Table 1), gave signed consent, and were included in the study. Key exclusion criteria were subjects with chronic wounds, patients with underlying diseases judged to be of potential interference in the treatment, and pregnancy.

The study was conducted in accordance with the Declaration of Helsinki, the most recent version of ISO 14155, Food and Drug Administration, and International Conference on Harmonisation guidelines and good clinical practices for clinical research

Table 1. Inclusion/exclusion criteria

Inclusion criteria

- Subjects presenting with 1–25% TBSA deep partial or full-thickness burns requiring skin graft
- At least 1–10% TBSA available for grafting that could be considered for study site selection (intact, healthy peri-wound area around entire portion of this burned site)
- Both genders with age ≥ 18 yr but < 70 yr
- Signed informed consent

Exclusion criteria

- Subjects with chronic wounds, dermatologic skin conditions, or necrotizing disorder
- Subjects on mechanical ventilation
- Subjects diagnosed with underlying disease(s) (HIV/AIDS, cancer and severe anaemia) judged by the investigator to be a potential interference in the treatment
- Subjects treated with systemic glucocorticosteroids, except those taking occasional doses or doses less than 10 mg prednisolone/day or equivalent
- Use of immunosuppressive agents, radiation, or chemotherapy within the previous 30 days
- Known allergy/hypersensitivity to any of the components of the investigational products
- Subjects with physical and/or mental conditions that were not expected to comply with the investigation
- Participation in other clinical investigation(s) within 1 mo prior to start of the investigation
- Pregnancy

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

in the United States. The final investigation protocol and patient information and consent form were approved by an institutional review board.

Interventions

The enrolled subjects were randomized into two groups for either treatment with Mepitel One or Bridal Veil and staples. Randomization was performed at each of the four centers that participated in the study and not centralized. The randomization took place in the operation room at the time of grafting. This was achieved by the use of sealed envelopes that were opened at the time of randomization, using schedules that ensured equal numbers of patients were placed into each treatment group across all sites.

For both treatment groups, donor skin was harvested between 0.010 and 0.012 inch thickness and the skin was meshed at a 1:1 to 3:1 ratio. After the split-thickness skin graft was applied to the wound, Mepitel One or Bridal Veil and staples was placed over the graft and over a margin of the surrounding healthy skin.

Outcomes Measured

Baseline demographic data (age, gender, race, and medical history) and details of the wound history (type of burn, site, date of injury, percentage TBSA, wound appearance, and infection assessment [Table 2]) were recorded at the initial consultation.

Skin graft assessment was performed at day 7 (± 1 day) and day 14 (± 1 day). If the graft had $> 95\%$ take, before the 14 days, this was considered

the end of the study. The assessments included pain (prior, during, and after product removal), dressing removal (time and pain medication or other treatments required), graft take (adherence of the product to graft, separation of graft from wound bed, and graft loss), healing (percentage take of the graft, amount and type of exudate, suspicion of infection, and bleeding), peri-wound status; clinician input on handling; subject input on product, and adverse events.

The time and cost of staff were estimated by referring to www.indeed.com/salary for median salaries, and the start and stop time of treatment were recorded in hh:mm:ss. Cost data for the material used were estimated by collecting the quantities/units used and estimating the unit cost from the GHX database (www.ghx.com), the manufacturer's discount suppliers, and web vendors (the median value was reduced by 50% to reflect hospital costs more accurately). Photographs were taken to record the treatment status.

Statistical Methods

The condition of the subjects was considered fully evaluable if they finished each visit according to the protocol and a pain level as well as healing (graft take) assessment could be performed. If a protocol violation or deviation prevented an assessment being performed, whether it was for pain or for healing, the condition of the subject was considered only partially evaluable. However, the costing portion of the study was still obtained and either the pain or healing assessments performed if possible.

As the data were assumed to be skewed, appropriate nonparametric statistical analysis methods were used. All tests were two-tailed and conducted at 5% significance level. The primary efficacy variable was analyzed using the Mann–Whitney *U* test. Variables not regarded as efficacy were analyzed descriptively in the form of tables and listings. Additional summary tables were also used, including the median. For the cost calculations, descriptive statistics for time from randomization to opening the package or to start of application of dressing, as well as costs for staff time and materials are presented as means and standard deviations and medians and ranges.

In an attempt to assess comparability of staffing, treatment groups were compared with regard to time from randomization to the time the package was opened, and from the time of randomization to the time the application started using Wilcoxon Rank Sum tests. The total staff cost to apply the dressing product was computed as follows: the cost per staff member was computed as his/her time in hours involved with the task multiplied by the corresponding hourly salary; for each subject, the total cost was the sum of the costs of individual staff members. The average cost was the sum of total costs for subjects in a particular treatment group divided by the number of subjects in that group.

Total cost of materials was computed as follows: for each subject, the unit cost per item was multiplied by the number of items used, and the total cost was the sum of all materials' costs for that subject; these costs were then summed across subjects within a particular treatment group, and the average was that sum divided by the number of subjects providing data for that treatment group. Additionally, total cost per subject for materials and staff were summed. Differences between total staff costs, total materials costs, and the sum of materials and staff costs were tested for significance using Wilcoxon Rank Sum tests.

RESULTS

Study Population

The study was undertaken from March 2011 to December 2011. A total of 43 patients were assigned to the clinical investigation, of which three were considered either lost to follow-up or withdrawn. The “intention-to-treat” population included those patients ($n = 42$) for whom posttreatment randomization data pertaining to the primary objective were recorded. In all, 34 subjects were men and 8 women at an age range of 19 to 77 years and with a mean age of 38.0 years for the Mepitel One group and 42.3

years for the Bridal Veil and staples group. Patient demographics, characteristics, and burn type assessment are summarized in Table 2. For comparison of the two groups, Mann–Whitney *U* test was used to ensure that there were no significant differences between the treatment groups in terms of the extent of burn injuries at baseline.

Pain

Pain was measured using a 100-mm visual analog scale ranging from 0 (no pain) to 100 (worst possible pain) and was compared between the Mepitel One group and the Bridal Veil and staples group at post-op day 7 (+/-1 day). Subjects were asked to mark the severity of their pain on the scale. The pain level was obtained at the beginning of the dressing change and there was no significant difference between the groups ($P = .1690$). The pain level at the midpoint of dressing removal was significant between the groups, with the removal of Mepitel One being less painful ($P = .0118$). At the end of the dressing change, there was no significant difference between the groups ($P = .0791$), although with a trend to Mepitel One being less painful. Overall it was observed that the pain value was very low for the group receiving Mepitel One at all time points (Figure 1).

Of the 43 subjects enrolled, 12 were premedicated prior to removal of dressings and study product (10 in the Bridal Veil plus staples group; 2 in the Mepitel One group). In at least 4 cases, titration of intravenous medication was necessary to complete the dressing change for staple removal. This implies

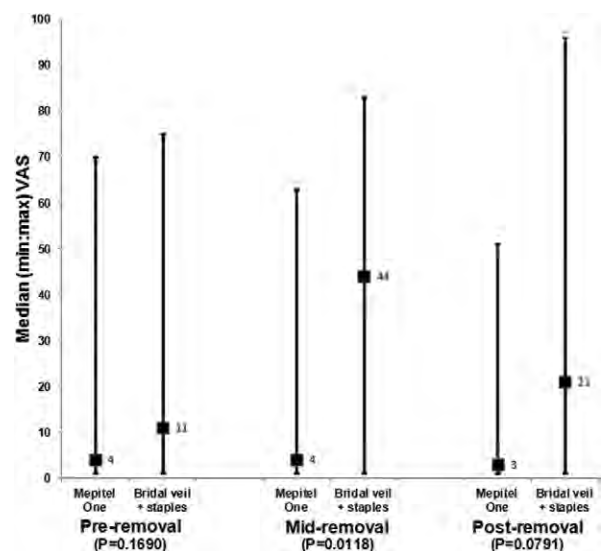


Figure 1. Pain of dressing removal 7 days post-operative measured using the visual analog scale (VAS) system.

that the pain levels during this procedure were so high that an extra dose of pain medication was necessary in order to tolerate the entire procedure with some level of relief from pain. The two premedicated subjects in the Mepitel One group were treated with oral analgesics with no titration of medication necessary.

Overall Costs

For the total of all costs, including time and unit costs, there was no statistically significant difference between the two treatment groups. However, there was a trend for lower costs with Mepitel One ($P = .1709$). There was a highly significant difference for the total staff costs in favor of Mepitel One ($P = .0064$) (Figure 2).

The time required for dressing application was comparable for both treatment groups ($P = .3152$). Less time was used for the removal of Mepitel One dressings. There was a statistically significant difference in favor of Mepitel One from the time dressing removal was started to the time dressing removal was completed ($P = .0005$). Bridal Veil and staples required 75% more time to remove than Mepitel One (Figure 3).

Dressing Removal

Dressing removal was assessed in terms of attachment of product to the graft and separation of the graft from the wound bed. Mepitel One showed less adherence to the graft at 11.8% compared to 25% for the Bridal Veil and staples. There was no separation of graft from the wound bed of patients treated with

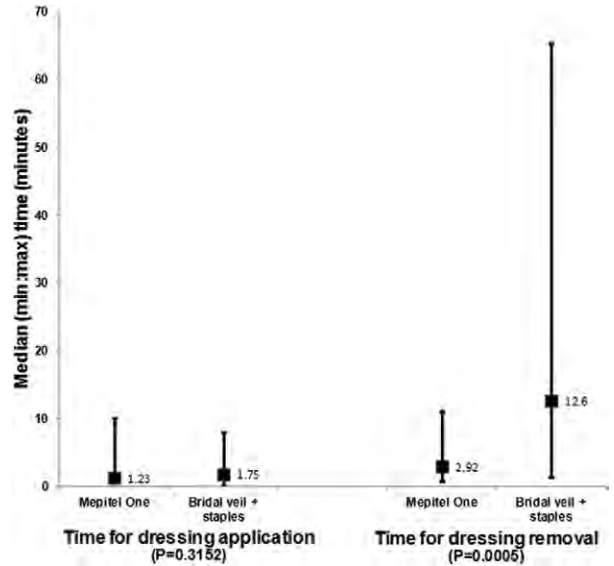


Figure 3. Time for dressing application and removal.

Mepitel One, whereas separation occurred in 15% of patients treated with Bridal Veil and staples.

Graft Take and Healing

Graft healing was defined as >95% take and was assessed at post-op day 7 (+/-1 day) after the removal of the dressing. No significant difference was noted in graft take assessment between the two groups with mean (SD) graft take of 98.1 (5.9)% in the Mepitel One group and 94.1 (20.5)% in the Bridal Veil plus staples group, with most grafts meeting the criteria for being healed at post-op day 7 (+/-1 day) ($P = .1449$).

Assessment of the graft take was defined in terms of the amount of exudate, the nature of the exudate, and the appearance of the graft. No significant differences were observed between the two treatments; however, Mepitel One performed slightly more favorably in all categories with 70% showing no exudate compared to 60% for Bridal Veil and staples.

Peri-Wound Status

Peri-wound status was assessed at the time of grafting and at the time of dressing removal (post-op day 7 (+/-1 day)). The variables assessed were turgor, dryness, flakiness, maceration, blistering, erythema, and warmth. With the exception of one subject who developed an infection of the graft site (Bridal Veil and staples), all subjects maintained a healthy peri-wound status. Some dryness and flakiness were reported in the majority of subjects in both groups, but this is to be expected with normal graft healing. No maceration, erythema, or blistering occurred

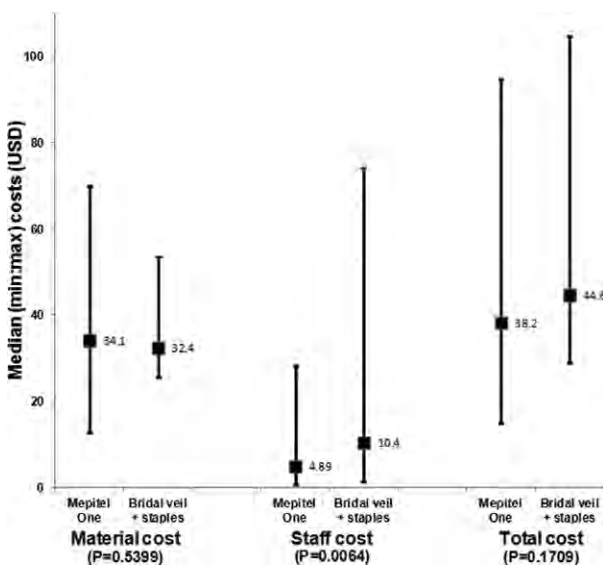


Figure 2. Total of costs.

Table 2. Patient demographics, characteristics, and burn injury assessment

Variable	Mepitel® One (n = 21)	Bridal Veil and Staples (n = 21)	P
Age	38.0 (18.0)	42.3 (16.0)	...
	30.0 (19.0; 77.0)	39.0 (19.0; 70.0)	...
Gender			
Male	16 (76.2%)	18 (85.7%)	...
Female	5 (23.8%)	3 (14.3%)	...
Race			
White	13 (61.9%)	11 (52.4%)	...
African-American	7 (33.3%)	9 (42.9%)	...
Other	1 (4.8%)	1 (4.8%)	...
General health before injury			
Underlying diseases	21 (100%)	21 (100%)	...
Major surgery interventions	17 (81%)	17 (81%)	...
Type of burn injury			
Flame	10 (47.6%)	10 (47.6%)	...
Scald	3 (14.3%)	2 (9.5%)	...
Contact	8 (38.1%)	9 (42.9%)	...
Burn injury assessment			
% TBSA	7.27 (5.41)	5.83 (4.38)	.3828
	5.00 (1.00; 18.00)	4.00 (1.00; 15.00)	
% partial	3.69 (5.30)	3.26 (3.99)	0.6906
	1.00 (0.00; 16.00)	2.00 (0.00; 14.00)	
% deep partial	1.25 (2.32)	0.38 (0.986)	.2287
	0.00 (0.00; 8.00)	0.00 (0.00; 3.50)	
% full-thickness	2.33 (2.33)	2.19 (2.96)	.4402
	2.00 (0.00; 9.00).	1.00 (0.00; 10.00)	

For categorical variables, n(%) is presented. For continuous variables, mean (SD)/median (minimum; maximum) n = is presented. For comparison between groups, Mann-Whitney *U* test was used for continuous variables.

in either group with the exception of the subject who developed infection, and this subject had mild erythema and warmth of the peri-wound skin.

Clinician Input

Clinician input was given on the dressing's conformability to the grafted site, ability to stay in place, ease of use, transparency, and the overall experience with the dressing. This input was gathered at the time of grafting, and post-op day 7 (+/-1 day), and post-op day 14 (+/-1 day), if applicable. Both groups had similar evaluations for most categories, with some categories being more favorable for Mepitel One. For example, in the post-op day 7 (± 1 day) evaluations, the conformability of Mepitel One was rated as "good" or "very good" in 44.4% and 55.6% of assessments, compared to 80% and 10% of assessments with the comparator regime. The ease of use of Mepitel One was rated as "easy" (50.0%) or "very easy" (50.0%), whereas that of Bridal Veil and staples was rated as "difficult" (20.0%), "easy" (55.0%) or "very easy" (25.0%). In terms of overall experience, Mepitel One was rated as "good" or "very good" in 38.9% and 61.1% of assessments, whereas the

comparator regime was rated as "good" or "very good" in 75.0% and 5.0% of assessments.

Subject Input

Subject input was received on the comfort of the dressing, conformability, and overall experience with the dressing. Most categories were similar in responses but there was a more positive trend toward the Mepitel One group. For example, in the post-op day 7 (± 1 day) evaluations, the comfort of Mepitel One was rated as "good" or "very good" in 42.1% and 57.9% of assessments, compared to 40.0% and 25.0% with the comparator regime. In terms of overall experience, Mepitel One was rated as "good" or "very good" in 21.1% and 78.9% of assessments, whereas the comparator regime was rated as "good" or "very good" in 45.0% and 15.0% of assessments.

Adverse Events

Various adverse events were reported in both treatment groups; the majority of these were considered as typical complications that develop in patients with burn injuries. One subject in the Bridal Veil and staples group developed an infection of

the skin graft which was subsequently resolved with antibiotic therapy. No serious adverse events were reported in either treatment group.

DISCUSSION

This study set out to evaluate the pain experienced at dressing removal for Mepitel One compared to Bridal Veil and staples when used as a primary dressing over split thickness skin grafts. The suggestion is that alternative methods of fixing skin grafts in place that avoid the use of staples might lower the pain experienced by patients requiring skin grafts, in particular when the staples or alternative method of fixing the graft is removed once the wound has healed. The overall performance of the dressings was also assessed by both the clinicians and patients, and the cost of both treatments was estimated to ensure that the alternative method of fixing the skin grafts would be clinically viable.

Mepitel One was shown to be less painful than Bridal Veil and staples, at the time of dressing removal, and this difference was statistically significant ($P = .0118$) at the midpoint of dressing removal. Overall, the removal of Bridal Veil and staples appears to require a much larger amount and stronger type of analgesic to meet the pain needs of subjects during dressing removal compared to that of Mepitel One. None of the subjects in the Mepitel One group required the intravenous pain medication that was needed in at least four cases of the Bridal Veil and staples group. This is important to consider in terms of length of stay, nursing time, and possible analgesic-related complications.

Although pain was the primary consideration of this study, the financial implications of an alternative method of treatment must also be considered, because the dressing must be economically viable when compared to the standard treatment; otherwise healthcare providers will be reluctant to take on the greater expense. Fortunately, Mepitel One showed lower overall costs than Bridal Veil and staples, although this was not statistically significant. So the use of the soft silicone dressing may be considered as a practical alternative to staples in terms of graft fixation. Another advantage of the alternative method was that the time taken for dressing removal was greatly reduced with Mepitel One, and this was reflected in lower staff costs that were statistically significant.

Mepitel One was also found to be comparable to the usual method of treatment (Bridal Veil and staples) regularly used at the participating centers in all of the clinician and patient assessments. From

a clinical perspective, it is essential that a successful dressing used on split thickness skin grafts allows wound healing and is easy to use; in both these respects, Mepitel One performed well, with 99% graft take compared to 93.1% for Bridal Veil and staples after 7 days post-op (+/-1 day) and with slightly better scores in all assessments of graft take. Clinicians rated Mepitel One as "very good" in 50% of cases in terms of ease of use, and this compares favorably with the 25% who rated Bridal Veil and staples as "very good." Mepitel One also performed better than Bridal Veil and staples in terms of stay on ability and conformability, both vital aspects of a successful dressing. The removal of Mepitel One was also more successful with lower adherence and no graft lift, while 15% showed graft lift with Bridal Veil and staples. A positive experience of the treatment regimen from the patients' point of view is important not least to encourage them to comply with treatment, so it was interesting to note that the patients' experience with Mepitel One was very positive with 78.9% rating the overall experience as "very good" compared to 25% of the Bridal Veil and staples group. Of the Mepitel One group, 57.9% also found the comfort of the dressing to be "very good" compared to 25% of the Bridal veil and staples group. From the patients' point of view, experiencing less pain, with a lower requirement for pain medication and the reduced time of dressing removal all lead to a better quality experience when using Mepitel One.

This study is a pilot investigation and as such has some limitations in terms of the numbers of subjects enrolled in the study and the time over which the study took place. Ideally a larger number of subjects, preferably with larger burn wounds, would give the findings more weight as many of the differences between the two study groups are quite small. In a larger study, the cost of treating pain should also be considered. Here pain was not included in the cost analysis, both in terms of extra medication and the extra nursing time spent on pain management. Including these in the analysis would give a more accurate measurement of the costs of the alternative treatments. Also, a longer follow-up period than the 14 days used here would have permitted the study to look at not only the wound healing, which in many cases had occurred after 7 days (+/-1 day), but also the amount and quality of scarring and the overall patient satisfaction with the treatment. Future studies should also capture the size of skin grafts used in the comparator groups.

Future research would be expected to involve assessment of scarring and the resultant healed skin such as any potential loss of skin flexibility depending

on the wound location. This research would ideally involve larger numbers of subjects and include a larger number of regional and possibly international burn treatment centers. In view of the increasing use of fibrin sealants for fixing skin grafts, it would be interesting to compare Mepitel One with this intervention in future research.

CONCLUSION

The results of this study indicate that Mepitel One should be considered as a clinically acceptable primary dressing for placement over skin grafts in the treatment of burns. Mepitel One demonstrated less pain, better ease of use, and a better overall experience for patients than the comparator treatment involving the use of staples. When the total costs were evaluated, Mepitel One was also less expensive and took much less time to remove, a major benefit to both patient and clinician.

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ABSTRACT

INTRODUCTION: Pyoderma Gangrenosum (PG) is a rare immunological disorder with infiltration of white blood cells into the epidermis, characterized by necrosis and excruciating pain. Diagnosis is made through a process of exclusion, which may delay proper treatment. Many patients (pts) are subject to surgical intervention and wound care that exacerbates the condition prior to diagnosis of PG. Between 2004 and 2010, 5 pts with PG were admitted to our burn treatment center (BTC). A wide range of treatment modalities were used on these pts.

METHODS: An IRB-approved retrospective study was initiated to investigate pts admitted to our BTC with PG. Collected data included: demographic information, onset of symptoms, time to admission to our BTC, time to diagnosis, length of stay (LOS), wound care, use of corticosteroids, and surgical interventions. Medical history was reviewed for predisposing diagnoses associated with PG.

RESULTS: The average age of the pts was 64.6 (43 to 81) years. There were 3 male and 2 female pts. Pts presented with symptoms on average 129.4 days prior to BTC admission, however, 1 patient (pt) had a rash for 1 year and a non-healing lesion prompted BTC admission. Removal of this pt provided an average onset of PG of 70.5 days. LOS averaged 24 days (range 3 to 40 days) and the average time to diagnosis was 18.7 days (range 5 to 43 days). The average involved area was 3.9% (range 0.5 to 7%) with 4 of the 5 pts having lesions on the lower extremities and 1 involving the abdomen. Predispositions included a history of inflammatory bowel disease in 2 pts, malignant melanoma in 1, and psoriasis in 1. Prednisone was administered to 4 pts and 1 of those 4 also received dapsons. Initiation of corticosteroids occurred 1.75 days after admission for 4 of the 5 patients. No corticosteroids were administered to 1 pt. Of the 5 PG pts, 3 had excision and/or skin grafting. Vacuum-assisted wound closure was used on 4 pts. There was 1 death associated with sepsis which was diagnosed prior to admission to our BTC.

CONCLUSIONS: Making the exclusionary diagnosis of PG is difficult and pts may receive improper care in the interim. Skin grafting may result in progression of lesions. Persistent wounds that don't heal with conservative therapy, especially those with pain disproportionate to the findings, should be considered for a diagnosis of PG. Prompt diagnosis and specialized care in a BTC may greatly improve outcomes for pts with PG.

INTRODUCTION

Pyoderma gangrenosum is a rare ulcerative skin condition of unknown etiology¹ and is often a diagnosis of exclusion. Trauma preceded lesions in 30% of patients, most frequently the legs. Lesions have been described at healed surgical sites and healed lesions have been noted to recur.² About one-half of patients with pyoderma gangrenosum have ulcerative colitis,³ Crohn's disease,⁴ polyarthritis,⁴ leukemias, pre-leukemias⁵ or monoclonal gammopathies. Males and females are equally affected and it has no racial predilection.¹ The pathophysiology may involve an immune system dysregulation of cytokines including interleukin 8 and marked neutrophil dysfunction. Pyoderma gangrenosum usually occurs in the fourth or fifth decades of life. Surgical management of the wounds often worsens lesions. Biopsy demonstrates massive granulocytic tissue infiltration. Crohn's disease management via total colectomy may or may not resolve lesions. The role of skin grafting is unclear, but may be more successful after immunosuppressive therapy. On review of the literature, therapy that has been used includes glucocorticoids, cyclosporine, azathioprine, methotrexate, mycophenolate, thalidomide, colchicine, cyclophosphamide, anti-TNF alpha antibodies, and minocycline.

METHODS AND MATERIALS

Following IRB approval, charts were reviewed from seven patients diagnosed with pyoderma gangrenosum over an eight year period. Data collection included documentation of underlying diseases associated with pyoderma gangrenosum, onset of lesions, extent of lesions, gender, and age. Treatment with medications and surgical management data was also collected for the seven patients. Demographic data are provided in **Table 1**.

Table 1. Seven Pyoderma Gangrenosum Patients

	Age	DAYS from Surgery to Diagnosis	LOS Post Grafting	%BSA
MEAN	66	70.5	11.5	3.9
STD DEV	12.8	23.7	8.4	1.9
Range	43-81	42-90	6-24	0.5-7.0

RESULTS

Only two of the seven patients had a diagnosis of inflammatory bowel disease and one of the seven expired from complications of sepsis. Six patients initially demonstrated lesions on their lower extremities and one patient at a surgical site. All patients presented with extremely painful non-healing necrotic lesions. Six were treated with systemic corticosteroids. Five patients had vacuum assisted closure (VAC) treatment with pain scores of 5.4 ± 2.8 before and 5.0 ± 2.8 after VAC placement. Pain scores prior to corticosteroid treatment were 6.2 ± 2.2 and were 4.9 ± 3.3 after initiating corticosteroids. Corticosteroids were used 7.8 ± 8.5 days (median: 5 days) prior to grafting. The most frequently used wound care products were Mepilex Ag™ in 4, Santyl™ in 6, Xeroform™ in 4, and SSD in 3. 5 Patients received excision and STSG. Multiple excisions were done in 3 patients.



CONCLUSIONS

Management of chronic wounds that occur in pyoderma gangrenosum requires the expertise provided by the burn team. Skilled surgical management and wound care after initiation of immunosuppressive therapy. Our experience with this condition has demonstrated:

1. The need to resist the temptation to excise and graft the chronic wound.
2. That corticosteroids are the most consistently recommended treatment.
3. That vacuum assisted wound closure may increase neovascularization.
4. Burn centers provide consistent management of chronic wounds.

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Burn Center Management of Operating Room Fire Injuries

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Approximately 100 operating room (OR) fires occur per year in the United States, with 15% resulting in serious injuries. Intraoperative cautery was frequently associated with OR fires before 1994; however, use of supplemental oxygen (O₂), ethanol-based products, and disposable drapes have been more frequently associated with OR fires. Fires resulting from cosmetic and other small procedures involving use of nasal canula O₂ and electrocautery have been described in six published reports. We report five thermal injury cases admitted to our burn treatment center because of fires during surgical procedures over a 5-year period. Two patients undergoing supraorbital excision experienced 2.5 and 3% TBSA involvement burns; in a third patient surgical excision of a nasal polyp resulted in a 1% TBSA burn; in a fourth patient an excisional biopsy of a lymph node resulted in a 2.75% TBSA burn; and the last patient was burned during placement of a pacemaker, with resulting TBSA of 10.5%. Two of the five patients required intubation for inhalational injury. Two patients required tangential excision and grafting of their thermal injuries. All patients had received local or parenteral anesthesia with supplemental O₂/nitrous oxide (N₂O) for surgical procedure. There are a number of ignition sources in the OR, including electrocautery, lasers, and faulty OR equipment. The risk of OR fires increases with surgical procedures involving the face and neck, including tracheostomy and tracheobronchial surgery. The common use of O₂/N₂O mixtures or enriched O₂ for minimally complex surgical procedures and disposable drapes adds to the risk of an OR fire: the O₂/N₂O provides a fuel source, and the disposable drapes trap the delivered gas. Electrocautery near an O₂/N₂O source resulted in the five thermal injuries and warrants careful reconsideration of technique for surgical procedures. (J Burn Care Res 2012;33:649-653)

Operating room (OR) fires are a potentially catastrophic threat to the patient and the surgical team. Commonly used materials and OR practices can result in OR fires. The true incidence of OR fires is uncertain because of a lack of consistent reporting in the absence of injury. Published data suggest that somewhere between 20 and 200 fires occur each year.¹⁻⁷ For surgical procedures requiring electrocautery in close proximity to

anesthetic gases, such as nitrous oxide or oxygen (O₂) supplementation, the risk of OR fires increases. To sustain a flame, there must be a potential fuel source, a readily available source of O₂, and a source of ignition. Forty-five case reports about injury as a result of OR fires have been published.¹⁻¹¹ These case reports suggest that tracheostomy and/or tracheobronchial surgery are the most common procedures associated with OR fires.^{2-7,12,13} We report a series of five patients transferred to our burn treatment center because of intraoperative thermal injury. These patients were not burned in procedures involving tracheostomy or tracheobronchial surgery.

Emergency Care Research Institute estimates that there are more than 100 OR fire cases in the United States each year with one to three cases reported weekly.⁷ Approximately, 15% of these cases are considered to be associated with a serious thermal injury

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to the patient.⁷ It is estimated that one or two deaths per year are associated with OR fires.⁷ As of 2003, California, Tennessee, and Washington are the only three states that require reporting of all hospital fires.¹⁴ Six other states require reporting of hospital fires only if a major service disruption or serious patient harm occurs.¹⁴ Over a 4-year period, the Food and Drug Administration recorded 167 OR fires as part of its data collection for equipment failures.¹ The American Society of Anesthesiologists' Closed Claims Database noted a marked increase in electrocautery-associated OR fires from 11% before 1994 to 44% after 1994, perhaps reflecting increased electrocautery use.³ Though the risk of electrocautery-associated fires is well known, fires still occur because of inadequate safety precautions, fire safety education, and prevention.

A review of the 45 published cases of OR fires noted that 10 of these involved pediatric patients and six involved cosmetic surgery.^{2-7,9-11,14,15} Further review noted that 37 fires were associated with an electrocautery unit and five with a surgical laser. Eighteen of these 45 patients had initial ignition of their endotracheal tubes, whereas 15 cases reported ignition of a surgical sponge, surgical drape, or gauze pad. Of note, alcohol solutions or patient hair was the fuel source initiating three of the OR fires. Thirty-three cases attributed O₂ supplementation as a causal factor for OR fires. There were six reported deaths (13%) from the published cases.^{2-7,9-11,14,15} These forty-five case reports failed to include important data regarding the nature of these injuries, including burn depth, potential for inhalation injury, and length of hospitalization.

CASE REPORTS

Our burn center has treated five patients who have been burned by OR fires. The patients range in age from 14 to 66 years and were transferred to our burn center from Pennsylvania, Maryland, Delaware, and New Jersey. These patients had an average TBSA burn of 3.95% and had an average length of stay of 12 days in the burn center. All five incidents involved cautery units, and all patients sustained burns to portions of the face and head. Additionally, two of the five patients suffered from inhalation injury and required mechanical ventilation.

Case 1. A 65-year-old woman presented with a basal cell carcinoma on her face requiring supraorbital excision. She received intravenous anesthesia and supplemental O₂ with a flow rate of 5 L/min. During

the surgical procedure, the electrocautery unit ignited a surgical drape within the surgical field.

She sustained a 3% (TBSA) partial thickness burn injury, of which 2.5% TBSA was located on her face and head and 0.5% TBSA was to her anterior trunk. On physical examination, the patient was found to have soot around her mouth and nose, singed nasal hairs, and a singed right eyebrow. The patient required endotracheal intubation prior to transfer to the burn center. Inhalation injury was confirmed by bronchoscopy.

The burn wounds were treated with topical therapy and did not require surgery. She received parenteral and oral analgesics for pain management. After 9 days, the patient was discharged home. The patient was followed up in the outpatient burn wound care center for 2 years for scar management and complications of posttraumatic stress disorder (PTSD).

Case 2. A 39-year-old woman underwent elective plastic surgery for the excision of three left periorbital lesions. Initially local anesthesia was attempted; however, patient discomfort warranted a change to intravenous sedation and supplemental O₂ via face mask. A handheld battery-operated disposable cautery unit ignited the O₂ face mask. Flames were immediately extinguished by shutting off the O₂ source and smothering the fire. Immediate first aid was initiated to the face with ice water, followed by normal saline irrigation. The wound was covered with sterile gauze in preparation for transfer to our burn treatment center.

The patient sustained a 2.5% TBSA partial thickness burn. The area of injury was the left periorbital area including left eyelashes and eyebrow, malar, and oral commissure. In addition, the nasal vibrissae were singed. During initial evaluation, the patient demonstrated progressive hoarseness and coughing. Risk of potential smoke inhalation required a diagnostic bronchoscopy that revealed no laryngeal or bronchial injury. Her wounds were managed with topical therapy and healed without surgical intervention. After 6 days in the burn center, the patient was discharged home. The patient was followed in the outpatient burn wound care center for scar management and significant anxiety disorder for 12 months postdischarge.

Case 3. A 14-year-old girl underwent surgical excision of a nasal polyp. She received total intravenous anesthesia (TIVA) and supplementary oral O₂ at 2 L/min. The electrocautery unit ignited a surgical sponge in the operative field, which then ignited the oral O₂ cannula. The cannula was immediately removed, and the O₂ was turned off. Wet sponges were applied to her face as immediate

first aid measures. The patient was then transferred to our burn treatment center.

She sustained a 1% TBSA partial thickness burn to her face, lips, and left nostril. On physical examination, black soot was found on the patient's mouth, tongue, and hard palate. Further evaluation revealed no smoke inhalation injury. She remained in the burn center for 24 hours. Though this was a small burn injury, the patient required follow up for PTSD.

Case 4. A 53-year-old woman underwent excisional biopsy of a right supraclavicular lymph node. The patient received TIVA; however, partial airway obstruction warranted supplemental O₂ at a rate of 6 L/min. While the electrocautery unit was in use, a flame was noted under the sheets to the left of the patient's neck, which then immediately spread to the drapes and the patient's face. The O₂ source was promptly discontinued. Immediate first aid was limited to the application of water to the patient's face.

The patient's airway was inspected by otolaryngoscopy in the OR revealing no evidence of upper airway injury. General anesthesia was then used to complete the procedure. Following surgery, the patient was extubated, placed on an O₂ face mask, and transferred to our burn center. Initial evaluation revealed a 2.75% TBSA burn to the left lower eyelid, nose, upper lip, left posterior and anterior neck, and the left ear. Follow-up bronchoscopy revealed no tracheal or lower airway injury.

Although initially the patient received topical treatment to the burn wounds, ultimately she required tangential excision and split thickness skin grafting to the left eyelid, nasal ala, right upper lip, and left malar regions. The patient was hospitalized for 24 days in our burn center. On discharge, the patient chose to be treated at an outpatient facility closer to her home. No further outpatient information was available for this patient.

Case 5. A 66-year-old man with cardiac dysrhythmias underwent surgical placement of an implantable pacemaker. An arc from the electrocautery unit ignited the end of the O₂ tubing and flames spread to the surgical drapes. The O₂ source was immediately shut off, the flame was smothered, and first aid was immediately initiated. The patient was intubated and transferred to our burn center.

On admission to our burn center, the patient was noted to have a 10.5% TBSA burn. Partial thickness injuries were identified on the face, neck, and ears. The eyebrows were singed, and soot was found in the oropharyngeal area on examination. Bronchoscopy revealed findings consistent with inhalation injury including edema of the vocal chords and damage to the tracheal and bronchial mucosa. The

patient remained on a mechanical ventilator for 14 days. Debridement of the burn wounds and application of a synthetic biological dressing was performed in the OR. The patient was discharged and followed through the outpatient burn wound care center. He required two surgical reconstructive procedures for microstomia within 1 year after burn injury.

DISCUSSION

To initiate a flame, all three components of the fire triangle must be present: an ignition source, an oxidizing agent, and a source of fuel. Ignition sources commonly found in the OR include electrocautery devices, battery-powered surgical cauteries, lasers, fiber optic cables, defibrillators, and faulty medical equipment.^{2-10,12,13,16} O₂, the most obvious oxidizing source, is available in room air (21% O₂) and with supplemental O₂ provided directly to the patient with concentrations up to 100%.^{7,17,18} Other oxidizing sources used in the OR are O₂/nitrous oxide mixtures.^{7,15,17} As the concentration of these oxidizers increases, the risk of fire igniting in the OR is greater.^{7,15,17,19} Many surgical supplies used in the OR are ideal fuel sources. These include cellulose, rubber, nylon, cotton, polyethylene, and volatile liquids that are in the immediate surgical field.^{7,12,13} Additionally, body hair can be a fuel source.⁷

Increased use of local anesthesia or intravenous sedation (minimal anesthetic concentrations [MAC] or TIVA) that permit same-day surgeries in minimally to moderately complex procedures often require the need for supplemental O₂. Thus, the risk of OR fires is increased.

Preference for local anesthesia or intravenous sedation commonly called MAC or TIVA often requires the need for supplemental O₂. Minimal to moderately complex surgeries including breast, hernia, and venous access surgeries are particularly sought for this mode of anesthesia as it permits same-day discharges.¹⁶ Because of high ambient O₂ concentrations used in these procedures with the proximity of the fuel and ignition sources, there is an increased potential for initiation of fire.

Research has demonstrated that reducing the voltage of the electrocautery unit from 3 to 1.5 V decreases the temperature from 1200 to 680°C, a temperature at which many surgical materials do not ignite.⁹ Therefore, attempts should be made to use the lowest electrocautery unit setting.^{9,16} Additionally, the time course at which ignition occurs has also been studied. Trials have demonstrated that ignition of cellulose drapes occurs at an average of 3.92 seconds and in as little as 0.5 seconds.¹⁰ OR fires may

occur even in non-O₂-enriched environments. For example, red latex rubber can be ignited in a 17% O₂ environment, which is less than the O₂ content of ambient air.⁷

Numerous publications outline methods to prevent OR fires. In one study, a dry sponge ignited after 3 seconds, whereas a wet sponge did not ignite until after 10 seconds. A practical suggestion would be to soak surgical sponges and gauze in saline.^{2,4,7,9,13} Other studies suggest the use of the lowest necessary electrocautery setting as well as shutting off supplemental O₂ for 1 minute before and during electrocautery use.^{2,4,6,7,19}

Standard draping defines the sterile surgical field. Standard draping over the face and neck can cause a collection of concentrated O₂ to occur in some instances. When comparing open face draping to standard draping technique, higher concentrations of O₂ levels were noted with standard draping.^{15,16} In one study, patients who received 1, 2, 3, or 6 L of O₂ per minute had a measured O₂ level under the draping of 23.5% after 30 seconds.^{15,16,19} The O₂ level decreased to less than 23.5% for patients who received 1 or 2 L of O₂ per minute after 60 seconds, whereas patients who received 3 and 6 L of O₂ per minute had levels that were still significantly elevated.^{12,18,19} Another suggestion was to substitute supplemental O₂ with a constant exchange of fresh compressed air.^{2,19} The results showed that under the drapes, the O₂ level fell as low as 14.9%, whereas the patient's pulse oximeter never fell below 96% when receiving 5 L of fresh air per minute and 97%, when receiving 10 L of fresh air per minute.⁵ This method demonstrated safe levels of O₂ concentration as well as adequate arterial O₂ saturation.

Many precautions have not been formally tested; however, observations have found them to be useful and relevant. One example is to let alcohol-based preparatory solutions dry completely before drapes are placed over the area to avoid trapping combustible vapors.^{1,2,7,12} Another easy step is to use a scalpel instead of an electrocautery unit whenever entering the trachea thereby eliminating an ignition source and the possibility of a fire.⁶ Other suggestions of fire prevention such as cautery safety could be considered common sense and implemented by making the surgical team aware that a risk of fire is eminent and caution should be taken. Recognizing the causes of OR fires will keep doctors, nurses, technicians, and anesthesiologists alert for possible hazardous combinations and lead to vigilance and prevention.¹³

Proper response to the fire is vital in this iatrogenic emergency. Lack of knowledge about what to do when a fire occurs results in worse outcomes. In the

case of a small fire, it is suggested that the fire is extinguished with a gloved hand or a towel.² The steps for a larger fire depend on the situation at hand, but it is reasonable to first remove the ignition source, then stop the flow of O₂, and remove and extinguish the burning materials.² After the fire has been put out or contained, the next concern should be to care for the patient.² The anesthesia team should restore breathing with air instead of pure O₂ until all possible sources of the fire or reignition have been removed.² Fire blankets are not recommended as they can trap the fire around the patient. Also fire extinguishers are not recommended because of the risk of infection and wound complications. However, if saline is not sufficient to put out the flame, a fire extinguisher may be necessary.^{2,7} Water-based extinguishers are ill advised because the water used is not sterile, and the conductivity of water poses a risk of electric shock.⁷ Dry powder extinguishers are problematic because the powder released is not water-soluble, is difficult to remove from the wounds, and irritates respiratory mucus membranes.⁷ The Emergency Care Research Institute suggests that a 5-pound carbon dioxide extinguisher be mounted on the inside of every individual OR.⁷ The carbon dioxide extinguisher leaves no residue as it smothers the fire and minimizes thermal injury through its cooling effect.⁷

The response to a fire can mean life or death. In the reported cases, there were two very similar incidents where electrocautery ignited an endotracheal tube. In the case where the surgical team did not know the proper safety procedures, the result was death of the patient, whereas the second surgical team was better educated on the proper safety response and was able to extinguish the fire with no harm to the patient or staff.⁷

Our patients sustained an average of 3.95% TBSA burns. All five cases were associated with surgery of the head, neck, or upper torso and involved a mask or nasal O₂ supplemental anesthetic technique. The patients required the multidisciplinary care of a burn treatment center including respiratory care, wound management, pain control, and psychiatric support for emotional distress. Two patients had inhalation injury diagnosed via bronchoscopy and required intubation. Most of the burns sustained involved the periorbital areas, nose, and ears because of proximity of the fire to the face. The wounds typically ranged from superficial to intermediate depth. In addition to topical antibiotic medication, these wounds were managed with biosynthetic dressings or split thickness skin grafting. Although the average percentage of burns was relatively small (3.95%), the mean length of stay was 12 days with a median of 9 days.

The average cost of care exceeded \$81,000. Subsequently, these patients were followed for at least a year and most had permanent scarring with PTSD as a result of their injuries. All cases led to litigation; however, the out-of-court settlements allowed the hospital and staff involved in the incidents to bear minimal financial loss.

These cases could have been prevented if there had been recognition of the inherent dangers posed in the OR environment. Although previous literature indicates endotracheal surgery and tracheostomy as the cause of OR fires, none of our cases involved this type of surgery. In fact, all had MAC or TIVA anesthesia. Suggestions such as O₂ discontinuation, using moist sponges, and compressed air instead of O₂ or using a different tool, such as a harmonic scalpel, could prevent future incidents. Over the past 10 years, the use of supplemental O₂ has been increasing as part of greater MAC and TIVA use. Perhaps these potentially devastating events can be avoided with awareness. However, when these fires do occur, burn center management is strongly advised.

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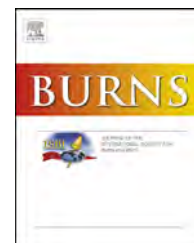
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Use of nebulized antimicrobial agents in burned and mechanically ventilated patients with persistent *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or *Enterobacteriaceae*

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ABSTRACT

Background: Nebulized antibiotics are used to locally treat colonizations of multi-resistant organisms. Prior systemic nephrotoxic antibiotic use with serum creatinine rises warranted an alternative therapy in 69 ventilator-dependent patients with persisting sputum cultures and need for ventilatory support.

Materials and methods: Following IRB approval, retrospective patient data were reviewed. Analysis included comparison of these 69 patients (71 treatments) to 142 Gram-negative infected burn patients matched for age and burn size.

Results: Mean pooled age and burn wound percent for the 71 triplicates ($n = 211$ patients) were 55.6 ± 18.3 years and $27.4 \pm 22.3\%$ burns. Fifty-seven of 69 (83%) patients had inhalation injuries and 54 of 69 (78%) patients survived. Nebulizations averaged 6.8 ± 3.3 days (range 3–12 days). Serum creatinine rose in 2 patients receiving colistimethate nebulizations, known to cause nephrotoxicity following nebulization. Triplicate comparisons via ANOVA noted prolonged ventilatory support ($F = 13.39$; $p \ll 0.05$) and length of stay ($F = 6.11$; $p \ll 0.5$). Variance was attributed to the sicker nebulized patients. Twenty-four inhalation injury-only triplicates further confirmed that nebulized patient subgroup was more ill.

Conclusion: Short duration antibiotic nebulization may allow higher intra-tracheal antibiotic concentrations and may facilitate weaning from the ventilator by reducing bacterial bio-burden.

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1. Introduction

Nebulized aminoglycosides have been used in the treatment of tracheobronchitis associated with intubation for inhalation injury patients for over 25 years [1–7]. Justification for use of nebulized antimicrobial agents for pneumonia was based on

pharmacokinetic studies demonstrating limited penetration of aminoglycosides into lung tissue of patients with pneumonia [1,8]. As with many therapeutic regimens used in critically ill patients, few randomized clinical trials have been done and few publications substantiate the merits of this therapy in such patients [3–5,9–11]. The most recent Infectious Disease Society of America/American Thoracic Society guidelines

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have changed the designation of nebulized antimicrobial agents from being viewed as unsubstantiated therapy to a designation of possibly effective therapy based on cases and small studies [14]. Resurgence in publications on nebulized antimicrobial agents also has increased this new acceptance of nebulized antimicrobial therapy [1,12,13].

Jean Klastersky first described the use of intra-tracheal aminoglycoside therapy as the administration of a 4 mL volume of normal saline containing 80 mg gentamicin instilled into the trachea of adult patients [2,4,7,10]. Other instillation studies were done by this author and others prior to the development of a method for aminoglycoside nebulization [4,5,7,10,12,15,16]. The use of nebulized aminoglycosides in thermal injury patients in the past was analogous to the endotracheal and pharyngeal decontamination procedures done in Europe during the 1980s and 1990s to reduce the incidence and recurrence of ventilator-associated nosocomial pneumonia [12,17-20]. The goal for its use in burn patients was to reduce the bioburden in the trachea and thus possibly reduce the risk of nosocomial aspiration pneumonias while on ventilatory support [13]. Measure of bioburden reduction can only be retrospectively assessed by apparent eradication of tracheal organisms following nebulization therapy. Nebulization of aminoglycosides has demonstrated no marked systemic aminoglycoside absorption [7,8,12]. Nebulized colistimethate has been associated with nephrotoxicity. Induction of bronchospasm and asthma attacks has been reported following nebulization of colistimethate [21-24].

The final concern with the use of nebulized antimicrobial agents is the presumed administration of an effective dose. With as much as 25% of the nebulization solution remaining in the nebulizer, an unknown quantity of antimicrobial agent exhaled, and distribution of the antimicrobial agent in respiratory equipment and disposable equipment, an assured nebulized dose remains uncertain. Given that an unknown concentration of antibiotic reaches the trachea and bronchi, inadequate nebulized dose for organism eradication and, emergence of resistance remain concerns with the use of this treatment modality.

2. Materials and methods

This was an investigational review board approved retrospective review of the use of nebulized antibiotics in the treatment of patients admitted to the burn treatment center with American Burn Association (ABA) referral criteria for admission [25]. The sole inclusion criterion was the use of a nebulized antimicrobial agent in the treatment of a patient admitted with an ABA referral criteria admission with evidence suggestive of tracheobronchitis impairing weaning from ventilatory support [25]. No patients treated with nebulized antimicrobial agents were excluded from analysis. Antimicrobial agent nebulization was performed by respiratory therapists using an Airlife jet nebulizer with a total time of treatment lasting approximately 20 min. Sputum changes as a result of antimicrobial nebulization were qualitatively assessed, but not consistently nor quantitatively.

Patients. All patients who had been admitted to the burn treatment center with an American Burn Association admission

criterion [25] and were screened retrospectively for treatment with nebulized antimicrobial therapy at the conclusion of their treatment for pneumonia and/or tracheobronchitis. All patients who had received a nebulized antimicrobial agent as part of their treatment for a bacterial respiratory tract infection were included in the analysis.

Inhalation injury. Inhalation injury was assessed by bronchoscopic visualization of the upper respiratory tree within 24 h of admission. Pulmonary medicine consultants perform this procedure looking for mucosal damage, evidence of blisters, etc. The ratio of the partial pressure of oxygen divided by the fraction of oxygen delivered (the $\text{PaO}_2:\text{FiO}_2$ ratio) was also used to assess acute lung injury and respiratory distress syndrome as part of the retrospective analysis of these data.

Definition of nephrotoxicity. The standard definition drug-induced nephrotoxicity is a 50% rise in serum creatinine and/or a 50% decline in the creatinine clearance by collection or calculation. This was proposed by Dr. Paul Leitmann and has remained as a standard definition of drug-induced nephrotoxicity [26].

Pneumonia and tracheobronchitis definitions. At the time of the study, the previous Centers for Disease Control (CDC) definition of pneumonia was used which is similar to the current Pnu-1 criteria [27]. All patients treated with nebulized antibiotics had tracheobronchitis at the onset of their treatment. Tracheobronchitis, by the CDC criteria, must be associated with a temperature $> 38^\circ\text{C}$, persisting cough, sputum production or wheezes in a patient with a positive sputum culture by aspirate or bronchial specimen in the absence of roentgenographic findings consistent with pneumonia. Pneumonia requires two or more of the following chest X-ray findings: (1) progression of infiltrate from at least two chest X-rays, (2) evidence of lung consolidation, (3) evidence of a new cavitory lesion. In addition the patient suspected of pneumonia must have at least one of the following: (1) fever $> 38^\circ\text{C}$, (2) white blood cell counts either $< 4\text{K}$ or $> 12\text{K}$, and (3) for elderly patients a marked change in level of consciousness. Finally, a suspected pneumonia patient must have 2 of the following: (1) purulent sputum or a change in sputum character, or increased requirements for suctioning of sputum, (2) new onset of cough, dyspnea, or tachypnea, (3) râles or bronchial breath sounds, (4) worsening gas exchange as noted by a $\text{PaO}_2:\text{FiO}_2$ ratio of ≤ 240 . Patients selected for nebulization did not fit the CDC criteria for pneumonia [27].

Isolated organisms. All Gram negative organisms isolated from covered suctioned catheter collections and bronchoalveolar lavage collections were reviewed for antimicrobial susceptibility data. Suctioned sputum cultures required the presence of white blood cells in the Gram stain. The resulting organisms and the minimum inhibitory concentration data available were collected for analysis. Culture history was obtained on all patients to determine the persisting organisms in sputum prior to the initiation of nebulization therapy and to determine qualitatively and retrospectively if nebulization of antimicrobial agents had resulted in apparent eradication of the organisms isolated prior to nebulization. The total number of organisms prior to nebulization was determined as well as any change in isolates with the nebulization. Susceptibility was determined using the Microscan Walkaway system and

sputum cultures were collected and processed in the routine manner of our institution.

Antimicrobial agents used. Antibiotic use for nebulization was at the discretion of the burn surgeon based on sensitivity data provided by the microbiology laboratory. All antibiotics were prepared from formulations for intravenous administration by the pharmacy. A specific dose of antimicrobial agent was mixed with a volume of normal saline to produce a dosage of antimicrobial agent in a total volume of 4 mL. Normally patients received 40 mg of tobramycin, 250 mg of amikacin, or 125 mg of colistimethate as 1 mL doses dissolved into a total volume of 4 mL. The nebulization was administered using the Airlife™ 002446 nebulizer (Carefusion) by the respiratory therapist following a protocol established by the pulmonary medicine physicians, respiratory therapy, and the pharmacy department. Nebulizations were continuous and humidification was not shut off during the nebulization process. Three antimicrobial agents were used as nebulization as was recommended by the IDSA guidelines. The three agents used were amikacin, tobramycin, and colistimethate [28].

Nebulization procedure. By protocol, respiratory therapists were empowered to give bronchodilators prior to nebulization of the antimicrobial agent should the patient present with bronchospasm during nebulization. The investigators did not consistently observe the nebulization of antibiotics. Bronchodilators were not consistently used as part of the protocol and were administered following assessment of bronchospasm by the respiratory therapist. Nebulizations were accomplished by instilling 4 ml of antimicrobial agent containing saline into the Airlife nebulizer and attaching the nebulizer to the ventilator to permit inhalation of the drug containing mist as a continuous nebulization over 20 min and concomitant humidification [29]. Pressure over the solution causes misting of the solution and instillation during inhalations. Most adverse effects are due to the irritation caused by the nebulized antimicrobial [29]; however, colistimethate is a prodrug which generates metabisulfite [22,24]. Metabisulfate is a known inducer of bronchospasm in patients with a history of asthma and warrants concern when using colistimethate for nebulization. Outside of the United States, colistin itself is available for infusion or nebulization thus avoiding this potential complication of therapy.

Assessment of response. As a retrospective study, only data extracted from the medical record was available concerning the response to therapy. All patients had tracheobronchitis or had progressed from pneumonia to tracheobronchitis prior to initiation of nebulizations. Based on the reviewed literature, the duration of nebulization was to be limited to 5–7 days. Treatment over the weekend or holidays prolonged therapy beyond the 5–7 day treatment goal in 5 patients. Thus the evaluation of therapy included the number of days of nebulization therapy as recorded, changes in white blood cells, temperature, heart rate, and respiratory rate. All assessments carried the caveat that causes other than infection could have caused the assessed changes. Chest X-rays were reviewed to confirm that patients did not have pneumonia at the time of treatment. Additional data were also collected such as computerized axial tomography scans that had been obtained concomitantly during the period of antimicrobial agent nebulization indicated that patients did

not have findings consistent with pneumonia. Mean difference in temperature and white blood cell count were used to assess response to antimicrobial agent nebulization such that a positive difference would indicate “benefit” from nebulization, while a negative difference would suggest “no benefit” from the nebulization. Extubation within 2 days of completing nebulizations was also assessed as a potential for the evaluation of the efficacy of this treatment modality. In addition, the apparent eradication of the organisms from sputum was used as an additional measure of “benefit” of nebulized antimicrobial agents in our patients. Changes in oxygenation/pulmonary function were assessed by PaO₂:FiO₂ ratio, review of chest X-ray findings, and assessment of the ability to wean the patient from ventilatory support as a result of nebulization therapy.

Post hoc analysis. For the 71 treatment courses of nebulized antimicrobial agent in 69 patients with isolation of either *Acinetobacter baumannii* or *Pseudomonas aeruginosa*, one question was whether this nebulized patient population represented an equivalent or more ill burn patient sub-group. Each nebulized treatment patient had been infected with *P. aeruginosa* or *A. baumannii* and they were matched with a comparable *P. aeruginosa* infected patient and a comparable *A. baumannii* infected patient with the same approximate age and total body surface area involvement. Data collected from the nebulized patients was also extracted from patient medical records for the two sets of patients for comparison to the nebulized patients. From these 213 patients/treatment courses (69 nebulization patients with 71 treatments and two sets of 71 patients with either *P. aeruginosa* or *A. baumannii* infection) demographic data were compared using ANOVA. A further data reduction was done by eliminating triplicates for which one in the selected group did not have an inhalation injury in order to compare patients with inhalation injury among the three groups. Many of the triplicates had only one or two inhalation patients in the triplicate with comparable age and size of burn. By removing triplicates that did not have three inhalation injuries, the number of triplicates was reduced from 71 to 24. These data were also subjected to demographic data analysis with ANOVA.

3. Results

Our verified burn treatment center admits approximately 475 patients per year with American Burn Association (ABA) criteria diagnoses. Patients receive standard resuscitation using the consensus resuscitation equation and surgical management according to ABA guidelines and best practice. Over a period of approximately 8 years, nearly 9000 patients were admitted for which a subset of ventilated patients with persisting tracheobronchitis warranted consideration of nebulized antimicrobial therapy. A total of 69 patients received 73 treatment courses with nebulized antimicrobial agents due to underlying acute renal disease, persistence of sputum production with multiple systemic antimicrobials, and for some as an attempt to prevent further exposure with systemic antimicrobial therapy. These patients demonstrated difficulty in weaning from ventilation due to persistence of tracheobronchitis and warranted consideration of nebulization of

Table 1 – Demographic data for 69 patients receiving 71 treatment courses with nebulized antimicrobial agents.

	All patients	Non-survivors	Survivors	t-Test
Number	69	15	54	
Age in years	55.6 ± 18.3	55.3 ± 18.3	56.5 ± 19.2	NS
%Burn surface area	27.4 ± 22.3	25.2 ± 21.6	35.8 ± 24.1	NS
Length of stay (days)	64.8 ± 35.8	63.2 ± 30.5	70.6 ± 51.6	NS
Onset of nebulization	37.6 ± 28.0	33.6 ± 23.7	50.9 ± 36.5	NS
Pre nebulization (P:F ratio)	285.5 ± 100.9	297.9 ± 97.5	240 ± 103.9	NS
Post nebulization (P:F ratio)	307.4 ± 110.2	307.5 ± 103.9	307.1 ± 130.7	NS

antimicrobial agents. This selected patient population constituted 65 thermal injury patients, a patient with toxic epidermal necrolysis, a patient with purpura fulminans, a patient struck by lightning, and a patient with calciphylaxis. Males represented 42 of the 69 nebulized patients (61%). Demographic data for these patients and stratification by survival status are provided in Table 1.

A total of 54 (76%) nebulized patients had had an inhalation injury. All 69 patients were intubated and required ventilatory support at the initiation of their nebulized antimicrobial agent therapy. Sixty-three (91%) of the 69 patients had previously received nephrotoxic antimicrobial agents systemically for long treatment courses prior to the decision to try initiation of nebulization therapy. Thirty-five (50.7%) had elevation of serum creatinine from prior nephrotoxic drug exposures warranting consideration of nebulized antimicrobial therapy to avoid recurrence of nephrotoxicity. For the remaining 49% of the patients, re-exacerbation of tracheobronchitis and difficulty weaning from ventilatory support warranted consideration of antibiotic nebulization. Assessment of serum creatinine at admission, ~5 days prior to nebulization, during nebulization, and finally ~5 days following nebulization demonstrated eight patients with elevated serum creatinine following nebulization with five occurring in the 15 non-surviving patients ($X^2 = 8.83$; $p < 0.05$). Prior nephrotoxic drug exposure was higher in the 15 non-survivors ($X^2 = 10.42$; $p < 0.05$). The modified Baux score [30] for these patients was 95 ± 27.2 with an intra-quartile range of 81.0–114.7 indicating that many of these patients were severely ill. Fifty-four of the 69 nebulized patients survived (78%). Fifty-seven of these patients had inhalation injury and stratification of these patients by inhalation injury demonstrated 45 of 57 survived (79%). As part of the retrospective review of data, 55 patients had sufficient pulmonary disease to have warranted computerized tomography scans of the chest. CT scans demonstrated findings consistent with pneumonia which had been treated with systemic antibiotics prior to initiation of nebulized antimicrobial therapy in 29 patients.

Nebulized antimicrobial agents were used for a total of 428 days of therapy as part of a total of 4472 days of burn care (9.5% of admission days) in the 69 nebulized patients. There were 29 treatment courses with amikacin, 36 treatment courses of tobramycin, and 8 treatment courses with colistimethate. Potentially nephrotoxic exposures included 58 patients who had been exposed to at least 8 days of vancomycin (84%), eight patients treated with amphotericin B for fungal infections (12%), 29 treated with intravenous aminoglycosides (42%) and 13 treated with intravenous colistimethate (19%). All but five of these 58 patients were exposed to at least one potentially

nephrotoxic drug (93%) and risk of further nephrotoxicity led to the decision to use nebulized antimicrobial agents as alternative therapy. Twenty of the 69 patients (29%) had serum creatinine > 1.5 at the start of nebulization most often representing the residua of prior nephrotoxic medication exposures.

A. baumannii was isolated in 46 of our nebulized patients (43%) and has been a problem organism in many hospitals including our burn treatment center for over 10 years. For the 46 patients infected with this organism, 33 had isolates already resistant to amikacin (66%) and 42 had isolates resistant to tobramycin (84%). For those patients with *P. aeruginosa* (21 patients) and the 14 additional patients who acquired *P. aeruginosa* isolates, two were initially resistant to amikacin (6%) and one was resistant to tobramycin (3%). Thus half of the isolates initially treated with nebulized antimicrobial therapy (33 *A. baumannii* and two *P. aeruginosa*) were already labeled as resistant to the aminoglycoside used as a nebulization. Resistance was defined based on the known ability of the specific agents to achieve effective systemic antimicrobial agent concentrations via intravenous administration.

Proteus mirabilis (four patients), *Klebsiella* species (six patients), and *Enterobacter* species (three patients) was also resident in the tracheas of burn patients. These Gram-negative organisms commonly colonize and infect intubated patients and may persist in tracheobronchitis leading to recurrence of pneumonia. No difference in distribution of *A. baumannii*, *P. aeruginosa*, or other Gram-negative bacilli was noted between survivors and non-survivors ($X^2 = 0.62$; $p > 0.05$).

Patients were treated for 6.0 ± 1.9 days with 54 of 69 nebulized patients surviving to discharge from the burn treatment center (78%). Initiation of nebulized antimicrobial agents occurred 38 ± 28 days after admission consistent with this being a late onset therapy for tracheobronchitis. Nebulization also was initiated at 27 ± 20 days before discharge again demonstrating its preferred use as part of the last phase of antimicrobial agent use. Duration of time following nebulization to extubation ranged from 1 to 4 days in surviving patients. Mean days was 1.8 with a median of 2 days; first quartile of 1 day and a third quartile of 2 days. On average, nebulization therapy decreased the white blood cell count (38 patients) and temperature (40 patients). Duration of hospitalization was 65 ± 36 days averaging 2.4 days per percent burned surface area again reflecting the high number of inhalation injuries and the severity of patient injury. The average partial pressure of oxygen to fraction of oxygen delivery ($\text{PaO}_2:\text{FiO}_2$ ratio) was 268 ± 94 during the days just prior to initiation of nebulization therapy and following nebulization this was

291 ± 101.3. Emergence of resistance was noted in three patients treated with the nebulized antimicrobial agents. All three of these patients had been treated for more than 7 days with nebulized antimicrobial therapy.

When stratified into survivors and non-survivors, there was no difference in the duration of nebulization, age, number with inhalation injury, length of stay, total body surface area burned, survival scores, PaO₂ to FiO₂ ratio before or after nebulization, days to onset of nebulization, change in white blood cells or temperature via Student's *t*-test. Use of the three studied antimicrobial agents did not show differences among survivors and non-survivors ($X^2 = 1.197$; $p \gg 0.05$); however, use of nephrotoxic antimicrobials and pressors prior to and during nebulization differed favoring non-survivors ($X^2 = 10.427$; $p \ll 0.05$). Distribution of the isolated organisms, including *A. baumannii*, did not differ ($X^2 = 0.624$; $p \gg 0.05$) among the three antimicrobial agents used. For five of 15 non-survivors, the organism at the start of nebulization had been eradicated by nebulization therapy and this was also true for 24 of 54 survivors.

Post hoc analysis. As expected there were no differences in age and TBSA among the three groups of 71 patients/treatments ($p \gg 0.05$). However, length of stay was markedly longer in the nebulized patient group when compared to the other two infected patient groups. Inhalation injury was noted in 34 of 71 comparison patients selected with *A. baumannii* infection and for 41 of 71 comparison patients with *P. aeruginosa* infection. Mean Baux score comparison of the three patient groups (nebulized therapy and the two comparators) ranged from 86.3 to 95.4 [30]. Analysis of variance for these modified Baux scores correcting for inhalation injury demonstrated no significant difference among groups ($F = 2.09$; $p \gg 0.05$) Mean length of stay, by contrast, was 65 days for the nebulized patients versus 34 days and 46 days for the *A. baumannii* and *P. aeruginosa* groups, respectively ($F = 16.11$; $p \ll 0.05$). Likewise, the average number of sputum cultures was 8.3 per nebulized patient versus 2.5 for *A. baumannii* patients and 3.5 for *P. aeruginosa* patients ($F = 28.36$; $p \ll 0.05$). Renal function did not differ among groups ($p \gg 0.05$). The nebulized patients required ventilatory support for 43.8 ± 28.2 days as compared to 18.9 ± 23.8 and 26.9 ± 28.8 days perhaps reflecting differences in the number of inhalation injury among the groups ($F = 13.39$; $p \ll 0.05$). Chi square analysis confirmed this difference with the lowest number being among the *A. baumannii* patients ($X^2 = 14.27$; $p \ll 0.05$). The initial partial pressure of oxygen to oxygen delivery (the P to F ratio) was markedly different with variance attributable to the nebulized group ($F = 3.38$; $p < 0.05$).

In order to clarify the above analysis further, the triplicates were culled if all three patients did not have an inhalation injury. This analysis eliminated 47 triplicates leaving 24 triplicates with documented inhalation injury. As before, there was no difference in age or TBSA among the 24 triplicates. Length of stay was on average 40 days and markedly shorter in the *A. baumannii* subgroup ($F = 4.06$; $p < 0.05$) with comparable time for the nebulized and *P. aeruginosa* groups (compare 67.8 days versus 66.5 days). For the nebulized inhalation injury only subgroup, the average number of sputum cultures was 10.7 per patient versus 4.6 and 6.2 for the *A. baumannii* and *P. aeruginosa* groups,

respectively ($F = 8.10$; $p \ll 0.05$). The ISS score and creatinine clearance were not different as were the P to F ratios among the three groups. For 25 patients, the initial organism in sputum was eradicated with nebulization and for 44 patients the initial organism persisted in sputum. Chi square analysis of survival status was not significantly different ($X^2 = 1.666$; $p \gg 0.05$). Gender was near equally distributed between those who eradicated the initial organism and those who did not ($X^2 = 0.539$; $p \gg 0.05$). Number of sputum cultures during the admission were significantly different favoring persistence among patients prolonged isolation of the organism ($T = 4.115$; $p \ll 0.05$) and length of stay ($T = 6.786$; $p \ll 0.05$) again suggesting that prolonged residence of the organism prior to nebulization was associated with persistence following nebulization. The average number of sputum cultures in persisters was 11.3 versus 2.6 for patients demonstrating eradication of the initial organisms. Duration of nebulization did not differ between patients who eradicated the initial organism and those who did not. P:F ratios before and after nebulization did not differ between those who eradicated their initial organism and those who did not. The distribution of organisms did not differ between those who eradicated the initial organism and those who did not ($X^2 = 2.973$; $p \gg 0.05$)

4. Discussion

The decision to use nebulized antimicrobial agents was often the result of persistence of sputum production, prior history of pneumonia recurrence, or history of renal impairment associated with systemic treatment with amphotericin B, aminoglycosides, or colistin. For 20 of these patients, risk for further nephrotoxicity warranted the use of antibiotic nebulization. Survival of 54 of 69 nebulization patients (78%) was no different from the survival findings of Palmer et al. [8].

For 29 of the 69 patients (42%), antibiotic nebulization resulted in eradication of Gram-negative organisms. Eradication of organisms seemed to correlate with duration of organism persistence prior to initiation of nebulization. Variance in actual antimicrobial agent delivered could not be assessed and likely contributed to persistence of organisms following completion of nebulization. No difference in infecting Gram negative organisms was noted for the three nebulized antimicrobial agents. Likewise, inhalation injury was equally distributed among the three nebulized antibiotic groups.

Certainly progression of renal dysfunction as a result of nephrotoxic systemic antibiotic re-initiation drove the decision to try antimicrobial nebulization. Twenty of these patients had prior episodes of antimicrobial agent-induced nephrotoxicity. Change in serum creatinine following nebulization could be linked to two patients receiving colistin nebulization.

A. baumannii has been an unwelcome resident for more than 10 years in many hospitals including our burn center [31,32]. This organism represented 43% of the sputum isolates in the nebulized patients. Chi-square analysis of *A. baumannii* distribution did not differ between survivors and non-survivors. Thus *A. baumannii* infection could not be attributed to differences in antimicrobial response. One question was whether nebulized antimicrobial agents would induce

resistance in patients receiving nebulizations as had been seen by others [8]. Three organisms emerged resistant to systemic antibiotic concentration goals following antimicrobial agent nebulization and were far fewer than reported by Palmer et al. [8]. Nebulization was kept as close as possible to less than 7 days. Emergence of resistance, noted in three patients, was associated with nebulizations lasting more than 7 days. Duration of therapy was the only available measure for emergence of resistance; however, the percent delivery of the nebulized dose remains unknown and more likely contributed to the emergence of resistance. The reporting of respiratory failure [24] induced by colistin resulted in the termination of nebulization in one patient who was treated for only 3 days.

The eradication of Gram-negative isolates occurred in only 42% of patients but was comparable to data in cystic fibrosis patients treated with antibiotic nebulizations [11]. Unknown delivered dose limited the assessment of the efficacy of the therapy as the number of milligrams of antimicrobial agent given was not determined. Neither measure of dose adequacy, nor amount of dose delivered was done and would need to be added to assessment in a prospective randomized trial. Symptoms of tracheobronchitis improved in at least 38 of the 69 patients (56%) consistent with references in the published IDSA ATS guidelines [14]. The potential benefit of nebulized antimicrobial agents as an adjunct to, or as completion of systemic antimicrobial therapy warrants further more rigorous investigation. There are limitations to this retrospective study including the absence of quantitative assessment of sputum production, which would also need to be added to a prospective trial. In the absence of a fixed protocol, duration of therapy was not controlled. A randomized trial of antimicrobial agent nebulization would require a specific order set with stated duration of therapy. Apparent facilitation of extubation was demonstrable in 54 of 69 patients.

Post hoc analysis using patient triplicates of matched patients indicated that the nebulized patients were sicker and that nebulization was chosen due to the slow response to systemic antibiotic therapy. Differences in the length of stay, ISS score, number of sputum cultures per patient and ventilator days all indicted that the nebulized patients were sicker. Extubation of survivors occurred in 54 patients at a median of 2 days following nebulization. 25% of the patients were extubated within 24 h of discontinuation of nebulization. 25 patients eradicated the initial organism of which 22 patients survived and 44 patients failed to eradicate the initial organism of which 33 survived. Eradication of the initial organism did not impact patient survival. Specific organisms also did not impact the eradication of the initial organism. Nebulization represents a treatment modality with potential benefits to ventilated patients with slow response to systemic antibiotics. Improved methods for antimicrobial agent delivery via new nebulization methods may further demonstrate the utility of this therapy in select patients with persistent tracheal colonization or tracheobronchitis.

Conflict of interest

The authors of this manuscript have no known investments in pharmaceutical companies manufacturing the antimicrobial

agents discussed in this paper and do not knowingly have investments in companies manufacturing disposable respiratory therapy equipment.

Dr. Patton has a relationship with Moelnlycke Health Care, which is a wound dressing focused company.

Drs. Ackerman, Guilday, and Haith do not speak for pharmaceutical companies nor receive income from consultations with pharmaceutical companies.

Ms. Reigart and Stair-Buchmann do not receive additional income from pharmaceutical companies outside of funding for IRB-approved clinical research.

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Pseudallescheria boydii Infection of the Brain

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Robert E. Guilday, Mary Lou Patton, and Linwood R. Haith, Jr.

THE MOST COMMON FUNGAL INFECTIONS associated with burn injury involve *Candida* spp., *Aspergillus* spp., and, more rarely, *Fusarium* and *Rhizopus* spp. We report here a patient who developed fungal brain abscesses caused by *Pseudallescheria boydii* that would have led to treatment failure had recommended therapy directed toward *Aspergillus* been used.

A 50-year-old patient with 64% total body surface area (TBSA) burns resulting from an explosion and fire had a complicated hospital course. Inhalation injury was documented by pulmonary medicine evaluation within 24 h of admission. He developed ventilator-dependent respiratory failure and pan-sinusitis. An echocardiogram demonstrated a patent foramina ovalis. Thirteen ring-enhancing brain abscesses were noted on computed tomography scan on the 25th post-burn day. Magnetic resonance imaging confirmed the diagnosis of brain abscesses (Fig. 1), and surgical drainage directed the selection of antifungal therapy. Intraoperative culture demonstrated *Staphylococcus aureus* and *P. boydii*.

These abscesses were treated initially with an echinocandin, but echinocandins are not effective against *P. boydii*; and abscess culture directed treatment with voriconazole. The patient recovered after long-term intravenous and then oral antifungal therapy.

Most central nervous system *P. boydii* infections occur in patients with predisposing conditions, immunosuppression, near-drowning, or trauma [1]. Chronic sinusitis may predispose individuals to infection with *Aspergillus* species and other filamentous fungi [2]. Multiple fungal isolates in bronchoalveolar lavage liquid, as was seen in this patient, are common in patients with chronic rhinosinusitis [3]. Fungal brain abscesses have been associated with a patent foramen ovale, as was noted in this patient [4]. Between 18% and 27% of persons in the community have this often-benign cardiac anomaly [4].

The importance of isolating *P. boydii* with aggressive drainage of brain abscesses cannot be overstated, as on the basis of bronchoalveolar lavage, the presumptive infecting

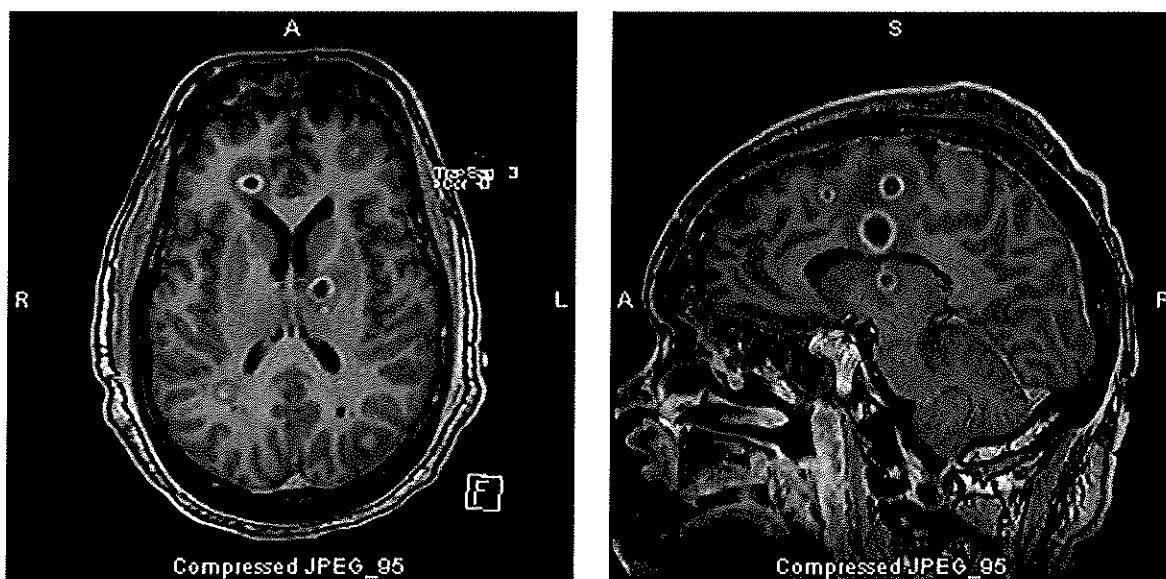


FIG. 1. Two views of fungal abscesses revealed by magnetic resonance imaging.

organism was *Aspergillus fumigatus* [5]. Antifungal therapy directed exclusively at *A. fumigatus* would have resulted in treatment failure and possibly death.

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ABSTRACT

INTRODUCTION: To improve blood glucose control in critically ill patients, an insulin infusion protocol was initiated for all critical care patients. In contrast to other critical care units, use of this protocol in the burn center resulted in multiple episodes of hypoglycemia and hyperglycemia. The only difference between our patients and patients in the other critical care units was lower hemoglobin levels. This led to investigation of the protocol.

MATERIALS AND METHODS: A prospective study with two POC monitors was developed to determine if the monitor itself had an effect on the blood glucose results in patients (N = 9) managed in the burn center. Paired sampling of POC was initiated using both the Accu-Chek (AC) and Contour (CN) bedside glucose-monitoring devices. Blood glucose determinations (N=1060) were obtained as per protocol. Laboratory blood glucose determinations (N=69) and hemoglobins were also collected and recorded. Resulting data was subjected to linear regression analysis with calculation of confidence intervals (see below). POC determinations were stratified as greater than or less than 8 g/dL (Range 5.6 – 11.1 HGB) and analyzed by a 2-way ANOVA.

RESULTS: Linear regression of the AC versus the CN POC demonstrated a wide scatter of points outside the confidence intervals for two POC devices. The resulting equation was $y = 0.9905x + 19.003$; $r^2 = 0.8424$. The AC overestimated the CN reading by 19 mg of glucose. ANOVA comparison of lab glucose, CN glucose, AC glucose as triplicates demonstrated the most variance in the AC POC ($F = 9.987$; $P < 0.05$). Stratification by HGB (< 8 g/dL $N = 27$; ≥ 8 g/dL $N = 32$) also noted greater variance with the AC POC associated with HGB < 8 g/dL ($F = 567.5$; $p < 0.005$). Looking at the triplicate values and hemoglobin noted again most variance attributable to the AC ($F = 80.89$; $p < 0.05$).

CONCLUSION: These data demonstrated less error with the CN POC device with HGB < 8 g/dL and demonstrated there is a potentially serious variance in resulting glucose concentrations when AC was used in patients with low hemoglobins.

INTRODUCTION

Van den Berghe et al showed that keeping blood glucose levels of critically ill patients below 120 mg/dL increased survival in intensive care settings by 54%.¹ Point-of-care (POC) blood glucose measurement systems are used to rapidly determine patient blood glucose levels and change in insulin dosage, but they have an inherent error of 15% to 20%. Burn center admissions with low hemoglobins have shown disparities between lab-drawn glucose levels and POC glucometer values.² The Ascensia Contour™ POC glucometer is not affected by low hemoglobin concentration in blood and was compared to the Accu-Chek™ POC glucometer; however, the Contour POC is for outpatient use only.

METHODS

Patients were screened in this IRB-approved prospective study.

Inclusion criteria. Patients requiring insulin infusion and glucose monitoring.

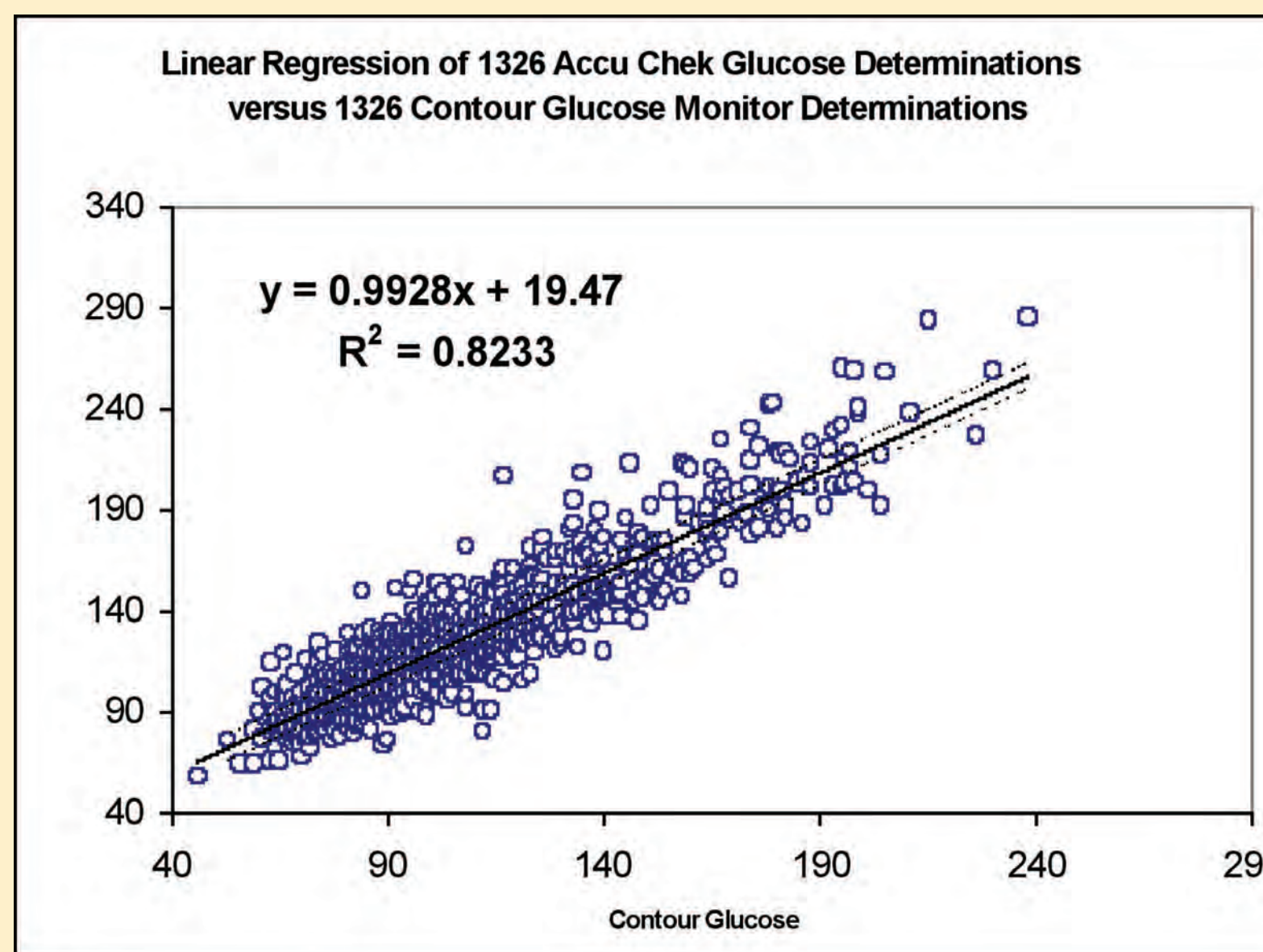
Exclusion criteria. Patients with greater than 70% total body surface area burn involvement.

Routine laboratory determinations. Blood glucose determinations and hemoglobin were drawn as part of routine care and monitoring.

Point of care blood determinations. Levels were obtained to permit blood glucose determination using both POC glucometers.

The two POC results were recorded with date and time. The Accu-Chek data was used to determine an insulin dose according to our institution's insulin infusion protocol with a goal of 80-120mg/dL.

Hemoglobin and glucose determinations. Only blood glucose determinations obtained within 6 hours of a hemoglobin were used in analysis of blood glucose determinations versus the two POC determinations.



Statistical analysis. Data were then subjected to linear regression. Confidence intervals were calculated using the F statistic (See figure above). 69 Laboratory glucose and paired POC levels were analyzed using ANOVA to determine if either of the two POC methods significantly deviated from the laboratory determination. POC data were stratified above or below the median hemoglobin and subjected to two-way ANOVA. As a final analysis, blood glucose determinations for the highest 25% and the lowest 25% were analyzed to determine how hemoglobin impacted both POC glucometers.

RESULTS

Blood glucose POC levels (N = 1326) in 11 patients and 69 laboratory determinations (N = 69) were collected. The Accu-Chek overestimated 19 mg/dL of glucose on average (See Figure). Single-factor ANOVA demonstrated the most variance in the Accu-Chek POC levels ($F = 9.987$; $P < 0.05$). The median hemoglobin noted greater variance with the Accu-Chek POC ($F = 567.5$; $p < 0.005$). Comparison of the highest and lowest 25% of hemoglobin noted greater variance in Accu-Chek levels ($F = 281.6$; $p < 0.05$). A two-way ANOVA comparing the triplicate values demonstrated variance in Accu-Chek POC ($F = 80.89$; $p < 0.05$).

CONCLUSION

Thermal injury patients may often be severely anemic. The system used in the burn center resulted in episodes of hypoglycemia and hyperglycemia. The use of two glucometers demonstrated:

- Consistently higher Accu-Chek readings
- Frequent insulin drip changes and hypoglycemic episodes
- That Accu-Chek errors were due to low hemoglobin (Hgb)
- That the Contour was the more accurate POC at Hgb < 8 g/dL
- That the highest and lowest 25% Hgb glucose pairs confirmed the difference

We now use a new POC monitor correcting for low Hgb

¹ Van den Berghe GHA. The neuroendocrine stress response and modern intensive care medicine. *Crit Care Med* 1999; 25:7-16.

² Mann EA, Salinas J, Pidcock HF, Wolf SE, Holcomb JB, Wade CE. Error rates in blood glucose corrected in multiple commonly used point-of-care glucometers. *Journal of Trauma* 2000; 48:100-104.

ABSTRACT

INTRODUCTION: Purpura fulminans (PF) is a rare disease usually involving massive dermal and soft tissue hemorrhage and necrosis associated with SIRS and refractory hypotension. Between 2006 and 2011 our burn treatment center (BTC) admitted 7 patients with a diagnosis of PF. We noted 2 distinct forms of PF: infectious and levamisole-induced. All aspects of burn care treatment were used in their management.

METHODS: An IRB-approved retrospective study was initiated to investigate PF admissions to our BTC. Data collected from the medical records included: medical/surgical history, date of symptom presentation, date of admission, date of transfer to our BTC, time to diagnosis, length of stay, location of tissue necrosis, limbs amputated, suspected levamisole use, use of activated drotrecogin alfa, and deaths. Descriptive statistics were generated for these patients and treatment was reviewed.

RESULTS: There appeared to be delays in diagnosis as well as transfer to our BTC. The average time from admission to diagnosis at outside hospitals was 3 days. Transfer to our BTC occurred, on average, 8 days after admission to the outside hospital. Body surface area involvement with tissue necrosis was $31.2 \pm 20.7\%$ and length of stay (LOS) for these patients was 78.0 ± 43 days. The most common sites of necrosis were the arms, hands, legs, and feet. Drotrecogin alfa was used in 3 patients. Amputation was required in 5 patients and 2 patients expired from complications of their PF. The deaths were not associated with larger wound sizes with areas of necrosis on these 2 patients 8 and 33%. It appeared that levamisole exposure was responsible for non-infectious PF in 2 patients. These patients did not meet the criteria for sepsis and did not require pressors. Their wounds appeared to be more focal, involving the ears and digits. In addition to aggressive surgical treatment, numerous wound closure strategies were utilized.

CONCLUSIONS: Early diagnosis of this cryptic disease may be difficult. However, once diagnosed, aggressive management in a BTC setting may promote improvement of limb salvage and survival. There appears to be a non-infectious form of PF associated with levamisole adulteration of illicit drugs.

INTRODUCTION

Purpura fulminans (PF) is a disease of uncertain origin causing microvascular thrombosis, death of skin, and underlying soft tissue.^{1,2} PF patients may present with myalgia, lightheadedness, high fever, and signs and symptoms consistent with early sepsis often requiring pressor support. Infectious causes of PF include: Group A hemolytic *Streptococcus*, *Legionella*, *Enterobacteriaceae*, and other pathogens.^{3,4} Non-infectious causes have included levamisole, a contaminant in cocaine, malignancy, autoimmune diseases, and transplant rejection.⁵ PF may be distinguished from other vasculitides by tissue biopsy; however it remains a diagnosis of exclusion. Early diagnosis may permit the use of plasminogen activator products, high dose corticosteroids, plasmapheresis, immunoglobulins, and even activated protein C to limit extension of skin lesions and soft tissue destruction.^{2,5} Management of complex burn wounds has led to the use of innovative therapy through the use of vacuum assisted wound closure and bioengineered wound dressings.^{2,6,7} In the past, the burn surgeons have received PF patients late in their care for skin grafting, management of complicated wounds, and amputation of limbs.^{1,2} The burn center provides a unique opportunity for early intervention due to interdisciplinary wound care that involves nurses, wound technicians, and technically skilled surgeons who bring a team approach to the care of the patient.

METHODS AND MATERIALS

Following IRB approval, charts were reviewed from eight patients diagnosed with PF over a six year period. Data collection included documentation of underlying diseases, history of drug abuse, onset of lesions, extent of lesions, gender, and age. Wound management and skin grafting were recorded. Patient charts were reviewed and data were collected for analysis. Demographic data are provided in **Table 1**.

Table 1. Demographic Data for Eight Purpura Fulminans Burn Center Admissions

	Age	Days to Transfer	BTC LOS	%BSA For Lesions
MEAN	43.3	5.8	67	44.0
STD DEV	6.3	3.5	48.9	29.8
Range	31-49	4-11	19 to 125	13.7-59

RESULTS

Six of the eight patients were female and two of these patients had lesions secondary to the use of levamisole tainted cocaine in the recent past. Two of the eight patients expired as a result of complications of PF. Removing two outliers, the time to diagnosis was 6.8 ± 4.1 days (range 2 to 12 days). There were diffuse differences in underlying diseases/habits among the patients. Hepatitis C was present in 2 patients, 3 had a history of intravenous drug use (2 with cocaine specifically), and 6 were smokers. During their admission, 5 patients required hemodialysis and 6 required ventilatory support indicating the degree of illness associated with PF. Surgical management included amputation (n = 6), skin grafting (n = 5), and use of vacuum assisted wound closure (n = 6). Wound dressings included the use of Mepilex Ag™ (n=6), Acticoat™ (n=3), Aquacel Ag™ (n=3), mafenide soaks (n = 5), silver sulfadiazine (n = 8), and Xeroform gauze (n = 6). CEA, Integra, EzDerm, & Oasis™ were also used on individual patients. Two patients who had been exposed to levamisole had loss of apical tissues, including ears, nose, and fingertips. One of these patients also had persistent inflammatory processes in her donor sites resulting in delayed healing. Interestingly, physical trauma immediately preceded the illness that led to the diagnosis of PF in the two patients that expired. One patient injured their hand following a fall in an industrial freezer and the other had a puncture wound to the foot from a carpet tack.



CONCLUSIONS

PF is difficult to diagnose and delay in transfer to a qualified burn center makes treatment options more complex. Early surgical intervention with amputation, and meticulous wound care are key to the successful treatment of PF. Amputation was required in 75% of our patients.

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Abstract

INTRODUCTION: The recently observed increases in the isolation of Methicillin-resistant Staphylococcus aureus with minimum inhibitory concentrations (MIC) ≥ 2 mg/L have caused some to advocate increasing the VT to 10 – 15 mg/L or even higher for increased efficacy. Normal monitoring is to obtain only a VT however for 68 patients 116 vancomycin peak (VP) and VT were obtained. This project evaluated the relationship of serum concentration time data and toxicity/efficacy.

METHODS: Using these VP and VT data, serum concentrations at 0.25, 1, 1.5, 2,4, 6, hours and midway through the dosing interval were estimated using 2-compartment pharmacokinetic data from data published by Rotschafer et al in 1982. These estimates and the VP and VT concentration were computer fitted with the goal of less than a 5% change in each VP and VT and an r-value in excess of 0.988. Patient data were stratified by increments of 50ml/min creatinine clearance from < 50 to 250 ml/min and by VTs of <5, 5-10, and >10 mg/L.

RESULTS: Resulting pharmacokinetic parameters were compared with the 1982 data. Time to negative sputum cultures, duration of therapy, time to normal white blood cell count, temperature and surface area burned did not differ among the stratified VTs ($F < 1$; $p \gg 0.05$). Chi-square analysis did not demonstrate greater risk of nephrotoxicity with rising VT ($X^2 = 5.555$; $p = 0.06$). Pharmacodynamic parameters were analyzed as well. The percent time over MIC (MIC = 1.75) interquartile range (IQR) was 89.82 to 93.34 predicting nearly 100% clinical response while the area under the serum concentration time curve divided by the MIC of 1.75 demonstrated an IQR of 235.8 to 412.5 indicating a little more than 25% of these 68 patients would have a clinical response. Using time to normal temperature, white blood cell count, heart rate, outcome from vancomycin therapy was assessed and no relationship could be demonstrated using Analysis of Variance ($F < 2$ for all parameters; $p \gg 0.05$).

CONCLUSION: These data indicate that there is no clear prediction of vancomycin success or nephrotoxicity following analysis of the obtained vancomycin peak and trough concentrations and subsequent exhaustive pharmacodynamic analysis.

	AGE	Weight	BSA	%BURN
Rotschafer	0.5± 0.3	2.7-13.4	15.6-110	13.3-183
NRSBTC	0.2± 0.06	3.1-13.6	14.6-95.5	14.6-273

INTRODUCTION

Vancomycin and trimethoprim sulfamethoxazole are commonly used agents for the treatment of methicillin-resistant *S. aureus* pneumonia (SAP). Many question vancomycin's potency and efficacy for bloodstream infections, endocarditis, and pneumonia. Inconsistent vancomycin lung penetration and the upward drift in minimum inhibitory concentration (MIC) over the past 5 years is worrisome. Troughs greater than 10 mg/L were expected to increase lung penetration with limited nephrotoxicity. Recent data has demonstrated nephrotoxicity (vancomycin troughs > 10mg/L).¹ Imipenem cilistatin "protects against" vancomycin nephrotoxicity.¹ We assessed vancomycin efficacy and toxicity in light of this data and recommendations.

1. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009; 49:507-14.

MATERIALS AND METHODS

68 patients with 116 peak and trough vancomycin concentration pairs and SAP were retrospectively identified in this an IRB approved protocol. 28 SAP patients with only trough concentrations were also included as separate study population.

Assessment of SAP

SAP required a purulent sputum, tachypnea, fever (temperature > 99°F), tachycardia, leucocytosis or leucopenia and a positive chest x-ray. Days of vancomycin and positive cultures was recorded in days and if no follow-up cultures, two days were added.

Table 1. Patient Demographics for Vancomycin Patients

	Age	Weight	Creat CI	Daily Dose	Each Dose
Demographics for 68 Vancomycin Peak/Trough Patients					
Average	42.5	87.4	141.7	27.7	12.2
STD DEV	18.3	21.5	73.0	9.6	3.0
Demographics for 28 Trough Only Vancomycin Patients					
Average	46.9	80.8	99.7	32.4	13.8
STD DEV	23.4	22.8	48.7	9.3	2.9
Comparison of Populations					
t-test values	0.998	1.437	3.479	2.447	2.581
p-values	0.31	0.15	<<0.05	0.015	0.011

Assessment of Vancomycin Concentrations

Vancomycin serum concentrations were obtained at one-half hour prior to and following a one hour infusion. Seven simulated vancomycin values calculated from microconstants previously published which were "fit" with a stripping program (JANA, statistical consultants) with r-value's > 0.9880, and less than a 5% increase or decrease in the peak or troughs. Cockcroft and Gault creatinine clearance was corrected for body weight. Serum creatinine was assessed at day 10 or at discharge. Concurrent nephrotoxic medications were recorded.

Pharmacokinetic Assessment

Pharmacokinetic parameters were used to calculate the area under the serum concentration curve with correction for a 1 hour infusion. Percent time over the minimum inhibitory concentration (%T>MIC) was calculated for MICs of 1, 1.5, 2.0 and 5.0.

MATERIALS AND METHODS (continued)

Assessment of Vancomycin Treatment Success

Eradication of SAP symptoms or change to linezolid, was used to assess vancomycin treatment response. Statistical analysis: Median and intraquartile ranges were determined for continuous data. Variance directed the use of student's t-test comparisons. Skew and kurtosis assessed normal distribution. Data were stratified by trough concentration (<5 mg/L, 5 to 10 mg/L, and > 10 mg/L), creatinine clearance (in increments of 50 mL/minute), and total daily vancomycin dose (in grams per day, mg/kg/day, and mg/kg/dose).

RESULTS

Demographic data are provided in Table 1 to the left. Time to negative culture was not significant ($F < 1.0$; $p \gg 0.05$; $F = 2.638$, $P > 0.05$) for the 68 nor the 28 patient groups, respectively. Duration of therapy, time to normal WBCs, and time to afebrile were not significant for the creatinine clearance or trough stratifications ($F < 2.0$; $P \gg 0.05$) for both populations. TBSA did not contribute duration of fever, WBCs, or therapy for creatinine clearance or trough stratifications ($F = 1.496$; $p > 0.05$). 40 of 68 patients and 14 of 28 patients received concomitant imipenem cilistatin. For 3 of 68 patients and 6 of 28 patients eosinophilia and nephrotoxicity (interstitial nephritis?) were noted.

Burn patients often are also infected with Gram-negative bacteria but this effect in both creatinine clearance and trough strata was not significant ($X^2 = 1.897$; $p > 0.05$; $X^2 = 2.543$ $p > 0.05$).

Table 2 provides simulations of the Total AUC, and the %T>MIC based on 116 peak trough pairs from 68 patients stratified by 50 mL/min creatinine clearance intervals.

CONCLUSIONS

1. For all CLCR and trough strata, duration of vancomycin therapy, temperature, and WBCs were not impacted by higher troughs.
2. Imipenem cilistatin appeared to protect renal function in over half the patients
3. The %T>MIC predicted the high success up to 2 mg/L seen in our 68 peak trough patients.
4. For 3 of 68 patients, treatment failure correlating with %T>MIC and 9 of 28 trough only pts had treatment failure (slow response over 10 days) warranting change to linezolid.
5. Percent burn did not impact creatinine clearance or trough concentration

Table 2. 116 Vancomycin peak-T

	Total AUC	%T>MIC = 1.5	%T>MIC = 5.0
4 Patients with creatinine c			
Median	273.1	90.4	
IQ 25 -75	191.8-552.92	84.4-93.4	
28 Peak Trough Pairs creatinine			
Median	357.8	94.5	
IQ 25 -75	218.9-568.9	92.4-95.4	
32 Peak Trough Pairs creatinine c			
Median	267.6	93.7	
IQ 25 -75	192.6-301.4	91.5-94.4	
28 Peak Trough Pairs creatinine			
Median	267.8	93.4	
IQ 25 -75	208.7-290.1	92.7-94.6	
24 Peak Trough Pairs creatinine			
Median	160.9	91.2	
IQ 25 -75	148.5-225.9	88.5-92.8	

Evaluation of the Relationship Between Elevated Vancomycin Trough Concentrations and Increased Efficacy and/or Toxicity

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Isolation of *Staphylococcus aureus* with minimum inhibitory concentrations, 1 to 2 mg/L, suggests increasing vancomycin trough ranges, from 10 to 20 mg/L or even higher. Vancomycin troughs from 604 treatment courses from 560 patients with suspected or actual Gram-positive infection were analyzed with focus on potential toxicity/efficacy. Trough concentrations were required to be drawn within 15 to 45 minutes before the administration of at least the third vancomycin dose. Patients were retrospectively evaluated for their total daily dose and milligrams per kilograms per vancomycin dose. Data on the duration of vancomycin therapy, days to a normal temperature, and white blood cells were obtained. Data were stratified by trough concentration as <5, 5 to 10, and >10 mg/L to determine whether there was any relationship between response and trough concentration. Demographic data were obtained in 560 patients with 604 vancomycin treatment courses. For 361 patients with 379 separate treatment courses of vancomycin therapy no other nephrotoxic antimicrobial agent had been used. The greatest risk of vancomycin nephrotoxicity correlated with the duration of treatment. Using the log time to normal temperature, white blood cell count, heart rate, outcome from vancomycin therapy was assessed and no relationship could be demonstrated for the three vancomycin trough strata using analysis of variance ($F < 2.62$ for all parameters; $p > .05$). These data indicate that vancomycin trough elevation may not guarantee treatment success and that there may be no real benefit from higher vancomycin trough concentrations in thermal injury patients with burns <20% TBSA. (J Burn Care Res 2013;34:e1-e9)

Vancomycin has been a mainstay in the treatment of thermal injury patients with Gram-positive cocci infections. For a considerable period of time, vancomycin represented one of the most commonly used antimicrobial agents for the treatment of burn-related Gram-positive infections, including methicillin-resistant *S. aureus*.¹⁻⁷ The potency and efficacy of vancomycin in the treatment of bloodstream infections, endocarditis, and pneumonia has been

questioned by many clinicians who have proposed definitions for vancomycin treatment failure based on comparison studies of other antimicrobial agents with vancomycin.^{8,9}

Recommendations to treat serious methicillin-resistant *S. aureus* infections with troughs >15 and <20 mg/L because of increases in the average minimum inhibitory concentrations above 1.5 to 1.75 mg/L were based on the presumption that vancomycin has limited nephrotoxicity.^{1,10-13} Recent data in patients treated with these higher trough concentrations has demonstrated elevated trough nephrotoxicity (vancomycin troughs >10 mg/L) and the investigators noted that the cilistatin in imipenem cilistatin seemed to protect against vancomycin nephrotoxicity.¹⁴⁻¹⁷ Given these new controversies, we attempted to assess vancomycin efficacy and toxicity in light of this recent data, to attempt to define for ourselves what vancomycin treatment failure

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seems to be for our thermal injury patient population, and to further study Gram-positive cocci infections in relation to vancomycin trough concentrations. Though there are limitations of our sample size and it is a retrospective study, a less clear relationship of trough concentrations and outcome was demonstrated among thermal injury patients with an average burn size of 22%.

MATERIALS AND METHODS

Six hundred eighty-four trough concentrations were retrospectively identified and data collected after an IRB-approved retrospective study protocol. *Staphylococcus* species pneumonia had been previously reported for a group of patients with 68 troughs, and hence, they were excluded from analysis. Of the 622 remaining vancomycin trough concentrations, improper collection resulted in elimination of 18 troughs, leaving a total of 604 vancomycin trough concentrations from 560 patients that were drawn at the correct time and at steady state (Table 1). A single representative trough concentration was collected for each vancomycin treatment course or after dose increase. Gram-negative or fungal infections occurred concomitantly in 176 patients with 206 vancomycin treatment courses, including 37 patients who were treated with amphotericin B or aminoglycosides for more than 5 days. In a separate analysis, 361 of the 560 patients with 379 vancomycin treatment courses and no other nephrotoxic exposure were assessed for vancomycin nephrotoxicity.

Demographic Data Analysis

Patient age, weight, height, TBSA burn, initial temperature, heart rate, white blood cell count, and serum creatinine were recorded in a computer database spreadsheet capable of calculation of descriptive statistics, including skew and kurtosis for assessment of normal distribution. Cultures were reported positive at least as an initial culture in 443 of 460 patients. Categorical data were also collected from the 460 patients whose medical records documented the following underlying complications: ethanol exposure, 277 of 560 (49%); tobacco use, 239 of 560 (43%); hypertension, 194 of 560 (34.6%); drug abuse history, 43 of 560 (7.6%); myocardial infarction, 60 of 560 (10.7%); heart failure, 44 of 238 (7.8%); and diabetes mellitus, 78 of 560 (13.9%). Demographic data are provided in Table 2.

Days of Vancomycin Therapy and Days to Negative Gram-Positive Culture

For enrolled patients, the time to discontinuation of vancomycin therapy was recorded in days, and positive cultures were counted from the time of vancomycin initiation until failure to isolate the organism as noted in microbiology reports. For patients with a single positive culture and no follow-up cultures, 2 days were conservatively added to the last positive culture day based on our culture schedule and concern of reporting eradication of an organism after a single day of therapy. The burn treatment center culture protocol, at that time, required sputum, urine, and blood cultures on Mondays, Wednesdays, and Fridays.

Assessment of Vancomycin Treatment Success

In addition to eradication of signs and symptoms of infection, a change to another antimicrobial agent, linezolid in particular, was used as an assessment of vancomycin treatment failure.^{4,7,9,11,18,19} As a retrospective review, assessment of treatment success was limited to parameters that could be effected by other concomitant processes, including Gram-negative infection, surgery, and so on. We presumed equal noise would be distributed among the patients for time to negative Gram-positive cultures, resolution of fever, resolution of tachycardia, and resolution of leukocytosis/leucopenia in the face of the decision to discontinue vancomycin. Thus, the study design limited any firm assessment of vancomycin success.

Assessment of Vancomycin Treatment Failure

Linezolid use after vancomycin therapy (evidence of vancomycin treatment failure) was recorded. It was presumed that the discontinuation of vancomycin and the immediate initiation of linezolid would be the result of clinical findings consistent with vancomycin treatment failure. This represented the sole definitive indication of vancomycin treatment failure. A second set of criteria for vancomycin treatment failure was assessed based on consensus of thought leaders in the area, comparison studies with vancomycin, and comments made by speakers during presentations on vancomycin treatment. A consensus definition of vancomycin treatment failure as more than 5 days with symptoms of infection was agreed to by the burn treatment team; however, these criteria were not used in the decision process for continuing vancomycin therapy or initiation of an alternative

Table 1. Demographics stratified by vancomycin trough

	Age	Weight	TBSA	ISS	ClCr	Daily dose	Mg/kg/day dose
157 Patients with 170 treatment courses with vancomycin troughs <5 mg/L							
Mean ± SD	36.2 ± 16.2*	84.6 ± 26.3	21.2 ± 21	14.4 ± 10.9	124.1 ± 45.9	2141 ± 609.5	26.8 ± 8.6
Median	35	81.2	15.5	13	117	2000	26.3
IQ range	24–47	67.1–102.3	5–30	4–25	89–142	2250–3000	20.9–30.6
256 Patients with 281 treatment courses with vancomycin troughs ranging from 5 to 10 mg/L							
Mean ± SD	43.9 ± 17.3	82.5 ± 23.6	24.9 ± 23.8*	16.1 ± 14.3	116.7 ± 53.6	2318 ± 698.5	32.6 ± 10.8
Median	43	79.2	16.5	11.5	104	2000	31.6
IQ range	30.5–56.0	68.5–94.2	6.8–36.3	4–25	79.9–139.5	2000–3000	25.6–38.2
147 Patients 154 treatment courses with vancomycin troughs ranging from 10.1 to 15 mg/L							
Mean ± SD	59.2 ± 20.0	80.2 ± 20.9	18.2 ± 21.4	12.0 ± 12.3	76.9 ± 39.1*	1977.1 ± 692.5	28.4 ± 9.6
Median	61	78.3	10.0	9	72	2000	27.7
IQ range	47–75	66.9–89.0	3–25.1	1–17	50.9–93.0	1500–2000	22.1–36.2
F, P	F = 70.97; P << .05	NS	F = 4.562; P << .05	NS	F = 3.419; P << .05	F = 12.284; P << .05	NS

NS, not significant.

therapy. Patients with fever >38°C, elevated white blood cells, and persisting cultures after 5 days or more of vancomycin therapy were assessed using the above criteria as potential vancomycin treatment failures. No patient with isolated vancomycin-resistant Gram-positive organisms was included in the analysis, and the decision to treat with linezolid was not because of the sudden appearance of vancomycin resistant *Enterococcus* species.

Assessment of Vancomycin Concentrations

Trough vancomycin serum concentrations were obtained one-half hour after a one-hour infusion period. Total times for collection and vancomycin infusion as well as levels were preferentially selected after the first 3 days of therapy. Following changes in therapy or reinitiation of therapy, a second vancomycin level was included in

Table 2. Demographic data for 560 patients and stratification by trough concentration range

	Age	Weight	TBSA	ISS	ClCr	Daily Dose	Mg/kg/day dose
Demographic data for all 560 patients with 604 vancomycin trough concentrations							
Mean ± SD	45.6 ± 19.7	82.5 ± 23.8	22.2 ± 22.6	14.4 ± 12.9	108.8 ± 51.5	2182 ± 686	30.6 ± 9.9
Median	44	80.0	15.0	10	100.8	2000	29.2
IQ range	30.0–59	67.5–95.4	5.0–30.4	4–25	73.8–135	2000–3000	24.4–36.4
157 Patients with 170 treatment courses with vancomycin troughs <5 mg/L							
Mean ± SD	36.2 ± 16.2*	84.6 ± 26.3	21.2 ± 21	14.4 ± 10.9	124.1 ± 45.9	2141 ± 609.5	26.8 ± 8.6
Median	35	81.2	15.5	13	117	2000	26.3
IQ range	24–47	67.1–102.3	5–30	4–25	89–142	2250–3000	20.9–30.6
256 Patients with 281 Treatment courses with vancomycin troughs ranging from 5 to 10 mg/L							
Mean ± SD	43.9 ± 17.3	82.5 ± 23.6	24.9 ± 23.8*	16.1 ± 14.3	116.7 ± 53.6	2318 ± 698.5	32.6 ± 10.8
Median	43	79.2	16.5	11.5	104	2000	31.6
IQ range	30.5–56.0	68.5–94.2	6.8–36.3	4–25	79.9–139.5	2000–3000	25.6–38.2
147 Patients 154 treatment courses with vancomycin troughs ranging from 10.1 to 15 mg/L							
Mean ± SD	59.2 ± 20.0	80.2 ± 20.9	18.2 ± 21.4	12.0 ± 12.3	76.9 ± 39.1*	1977.1 ± 692.5	28.4 ± 9.6
Median	61	78.3	10.0	9	72	2000	27.7
IQ range	47–75	66.9–89.0	3–25.1	1–17	50.9–93.0	1500–2000	22.1–36.2
Analysis of variance for the three trough strata							
F, P	F = 70.97; P << .05	NS	F = 4.562; P << .05	NS	F = 3.419; P << .05	F = 12.284; P << .05	NS

*Indicates that variance could be attributed to the one specific trough group using the Scheffé test. NS, not significant.

the analysis with the patient only counted once. Correctly obtained levels, presumed to be at steady-state with preference for mid-therapy vancomycin levels, were criteria for acceptance as usable levels.

Assessment of Vancomycin Exposure

Vancomycin total daily dose in milligrams per kilogram per day (mg/kg/day) was assessed as well as the mg/kg per vancomycin dose. Both actual weight and adjusted body weight milligrams per kilogram doses were determined and stored for further analysis. Follow-up trough concentrations were reviewed in the patient medical records for possible vancomycin accumulation, but these troughs were not included in the analysis. Change in serum creatinine was assessed at day 10 of therapy, presence of >5 eosinophils in blood, and creatinine clearance at day 1 and at the conclusion of vancomycin therapy were assessed. Nephrotoxicity was also assessed for the 604 treatment courses for 560 patients. A separate nephrotoxicity risk analysis was done for 361 patients without GNR infection or prolonged treatment with nephrotoxic drugs. This analysis compared the above 361 patients with 189 patients with nephrotoxic drug exposures and/or Gram-negative infection.

Statistical Analysis

Mean values, standard deviation, median, and intra-quartile ranges were determined for all continuous data. Variance was determined to assess student's *t*-test comparisons, and skew and kurtosis in combination with the difference in mean vs median were used to assess the near normality of data distributions. Data are reported as mean \pm standard deviation (mean \pm SD). Data were stratified by trough concentration (<5, 5–10, and >10 mg/L), and total daily vancomycin dose (in g/day, mg/kg/day, and mg/kg/dose).

Post hoc Analysis

Because of the small sample size, patients were also stratified into survivor and nonsurvivor groups to evaluate the role of survivorship on vancomycin trough concentration differences. Given the wide range of TBSA burn, a final stratification of patients with $\geq 50\%$ TBSA burn were compared with patients with burns <50% again looking for a trough difference.

Much of the data converted to days of some parameter during vancomycin exposure demonstrated profound skew and kurtosis (Table 3). Data

Table 3. Raw parameters obtained from 560 patients and stratified by trough range

	Days to Neg cx	Days Vanco tx	Days to Afebrile	Days to White Blood Cell < 10	Days to Heart Rate < 91
Data from all 560 patients with 605 trough concentrations treated with vancomycin					
Mean	7.9	15.7	10.2	8.5	12.8
SD	9.8	15.6	11.8	8.6	16.4
Median	5	11	6	6	8
IQ range	1–10	7–19	2–13	2–12	3–15
Kurtosis	21.5	7.3	8.1	5.3	7.8
Skew	3.7	2.5	2.4	1.8	2.5
Number	443	560	540	541	512
Data from 157 patients with 171 troughs <5 mg/L					
Mean	6.1*	13.3*	9.5	6.8*	11.5
SD	5.9	12.1	11.5	6.6	14.4
Median	4	10	5	4	7
IQ range	1–9.3	6–16	2–12	2–10	3–13
Kurtosis	2.9	11.1	7.7	5.1	7.9
Skew	1.5	3	2.5	1.8	2.6
Number	124	162	153	155	142
Data from 256 patients with 281 troughs >10 mg/L					
Mean	8.3	17.4	10.8	9.6	14.4
SD	10.2	16.9	11.3	9.7	17.2
Median	5	12	7	8	9
IQ range	2–10.5	7–21	3–15	2–14	4–17
Kurtosis	10.7	14.6	3.9	18.7	22.2
Skew	2.9	3	1.8	3.1	3.6
Number	215	265	255	255	240
Data from 147 patients with 154 troughs >10 mg/L					
Mean	9.1	15.5	9.8	8.3	11.1
SD	12	16.4	13.1	8.2	16.7
Median	7	10	6	6	6
IQ range	2–12.3	6–18	2–10.3	2–12	2–11.8
Kurtosis	26.3	10	12.9	4.9	13.1
Skew	4.4	2.9	3.1	2	3.4
Number	104	141	132	132	130

were log transformed, which was noted to improve skew and kurtosis of the data (Table 4). For the raw data, skew was noted to be as high as 4.4 and kurtosis up to 13.1 warranting concern that statistical analysis might be compromised by the data distributions. Given the small sample, log transformation was done with resulting skews of 0.0 to –0.3 and kurtosis from 0.0 to –1.1. This improvement in distribution about the mean eliminated the need to discard outliers, which would further reduce the size of the sample. When these data were analyzed, log-transformed data were used (refer to statistical analysis at the bottom of Table 4).

Table 4. Log transformation of parameters used for evaluation of vancomycin treatment success

	Log Days to Negative Cultures	Log Days of Vancomycin Therapy	Log Days Until the Patient was Afebrile	Log Days Until the White Blood Cells Fell to <10	Log Days Until the Heart Rate fell to <91
Data from all 560 patients with 605 trough concentrations treated with vancomycin					
Mean	4.5	11.2	5.6	5.2	6.8
SD	3	2.2	3.2	2.9	3.3
Median	5	11	6	6	8
IQ range	1.2-10	7-19	2-13	2-12	3-15
Kurtosis	-1.0	-0.1	-0.9	-1.1	-0.6
Skew	0	0.2	-0.1	-0.2	-0.1
Number	443	560	540	541	512
Data from 157 patients with 171 troughs <5 mg/L					
Mean	3.7	10.1*	5.0	4.2	6.1*
SD	2.9	2.1	3.3	2.8	3.3
Median	4	10	5.0	4	7
IQ range	1-9.2	6-16	2-12	2-10	3-13
Kurtosis	-1.4	0.3	-1	-1.2	-0.8
Skew	0	0.2	0	-0.1	-0.1
Number	124	162	153	155	142
Data from 256 patients with 281 troughs >10 mg/L					
Mean	4.7	12.3	6.2	5.9	8
SD	3	2.3	3.1	3	3.2
Median	5	12	7	8	9
IQ range	2-10.7	7-21	3-15	2-14	4-17
Kurtosis	-0.9	-0.3	-0.9	-1	-0.5
Skew	0	0.2	-0.2	-0.3	-0.3
Number	215	265	255	255	240
Data from 147 patients with 154 troughs >10 mg/L					
Mean	5.2	10.8	5.1	5.1	5.7
SD	3	2.3	3.2	2.8	3.2
Median	7	10	6	6	6
IQ range	2-12.2	6-18	2-10.2	2-12	2-11.7
Kurtosis	-0.7	0	-0.7	-0.9	-0.3
Skew	-0.1	0.3	0.1	-0.2	0.1
Number	104	141	132	132	130
F-statistic	0.2749	3.550	1.246	0.434	3.097
P	>>.05	<.05	>.05	>>.05	<.05

*Variance attributed to this group of the three groups.

RESULTS

Demographic data for 560 patients with vancomycin usable levels and data from 605 treatment courses of vancomycin are provided in Table 2. Time to negative culture in days was compared for troughs <5, 5 to 10, and >10 mg/L for the 560 patients ($F = 3.159$, $df = 2$; $P < .05$). However, this data

favored patients with troughs <5 mg/L with statistical difference but clinically suspect. Students' t -test comparison of the <10 mg/L vs >10 mg/L strata was not significant ($T = 0.583$; $P >> .05$). Likewise, comparison of duration of vancomycin therapy ($F = 3.558$, $df = 2$; $P < .05$) indicated significance favoring the <5 mg/L vancomycin trough concentration patient population. Patients with troughs <5 mg/L had shorter courses and less severe infections. Students' t -test of the latter two groups also failed to demonstrate a difference in duration of therapy with levels over 10 mg/L ($T = 1.088$; $P > .05$). Time to a normal white blood cell count, a soft parameter given the number with concomitant infections again favored patients with troughs <5 mg/L ($F = 5.452$; $df = 2$; $P << .05$) and again represented statistical significance because of less severe infection. Students' t -test for those patients with greater than or less than 10 mg/L showed no difference in normalization of white blood cell counts ($T = 1.453$; $P > .05$). Finally, time to becoming afebrile was analyzed ($F = 0.715$, $df = 2$; $P < .05$). It did not differ for the three serum vancomycin trough concentration groups. Students' t -test noted no difference in resolution of fevers with troughs >10 mg/L ($T = 1.585$; $P > .05$).

To assure that any difference in these groups was not because of a difference in TBSA burn, analysis of variance was also done on the three vancomycin trough strata data demonstrating that TBSA burn did differ in the 5 to 10 mg/L group ($F = 4.562$; $P << .05$). Again, TBSA burn involvement was markedly different in the <5 mg/L vancomycin trough group (Figure 1). Stratification based on greater than or less than a 50% TBSA burn demonstrated no difference in the distribution of trough concentrations between the 84 patients with burns >50% and the rest of the patient population ($T = 0.7166$; $P > .05$). Days of therapy were more in these patients ($T = 3.177$; $P << .05$) and the parameters used for treatment success were statistically different for the more severely ill patient population.

Ethanol consumption was lowest in the >10 mg/L trough patients ($X^2 = 8.54$; $P << .05$), but the significance of this was uncertain. Tobacco use and illicit drug abuse was equally distributed among the three groups. Hypertension was more common in the <5 mg/L patients ($X^2 = 18.99$; $P << .05$) and history of myocardial infarction, heart failure, and diabetes mellitus was more common in the >10 mg/L group ($X^2 = 27.97$; $P << .05$). Underlying disease and habits differed among the strata and may have affected parameters such as the heart rate < 91 beats/min.

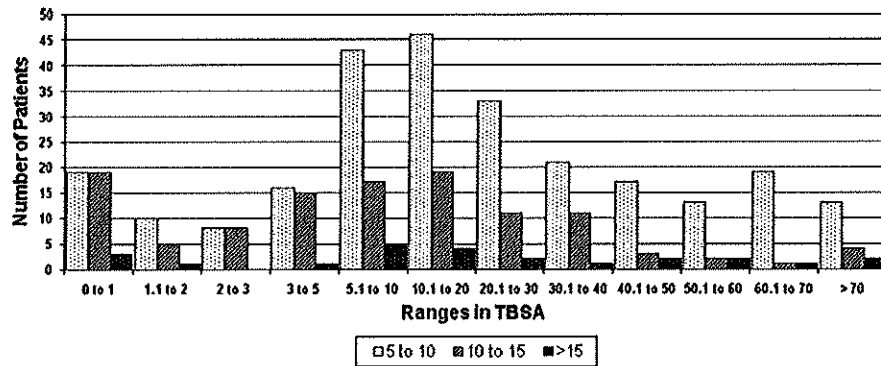


Figure 1. Distribution of TBSA burns for troughs <5, 5 to 10, and >10 mg/L.

For 391 of the 560 patients (69.8%), symptoms of infection persisted beyond 5 days. Of the 540 patients with complete data for this assessment, the possibility of discontinuing vancomycin, had we used the 5 days of therapy assessment of response as a definition of vancomycin treatment failure, would have approached 70% of the treated patients. Treatment failures following the first definition in our study were the 41 (7%) patients changed to linezolid. Using the 5-day criterion in the second definition of treatment failure described in the methods section above, the majority of the vancomycin treated patients (72%) would have been considered vancomycin treatment failures. By our change to linezolid criterion 7% of the patients were treatment failures indicating a 93% success rate with vancomycin therapy. From the 604 patients of whom the 361 patients with no Gram-negative infection were extracted, vancomycin success was 92%. The slow response of vancomycin after 5 days of therapy was noted in 70% of treated patients for which <1 in 10 were changed to linezolid.

Risk of nephrotoxicity was assessed using a standard definition as a rise in serum creatinine by >50% during treatment with vancomycin as proposed by Dr Leitman as referenced by Lodise et al.¹⁴ A total of 62 patients (11.1%) had a rise in serum creatinine indicative of some degree of renal function decline as a result of vancomycin therapy. Chi-square analysis demonstrated a greater risk of nephrotoxicity for patients with prior underlying renal impairment, resulting in rising vancomycin trough serum concentrations ($X^2 = 9.082$, $P < .05$). Distribution of baseline creatinine clearance is provided in Figure 2. Direct vancomycin nephrotoxicity was associated in 62 patients with an increasing percent of patients (<35%) for patients treated for more than 2 weeks. This is graphically presented in Figure 3 which provides the cumulative nephrotoxicity associated with each week of continued vancomycin therapy. Graphically described are those patients with Gram positive

only ($N = 361$) and both Gram-positive and Gram-negative infections with 204 vancomycin treatment courses in 189 patients. Subanalysis of patients receiving vancomycin concomitantly with imipenem cilistatin in the 189 patients exposed to vancomycin 204 times revealed that cilistatin was protective only one third of the time. Trough concentrations between the Gram-positive infected and both Gram-positive and Gram-negative infected patients did not differ ($T = 0.2451$; $P >> .05$). Nephrotoxicity in burn patients is multifactorial and differences in nephrotoxicity reflected concomitant drug exposures, greater TBSA involvement ($T = 7.768$; $P << .05$), underlying hypertension ($X^2 = 13.357$; $P << .05$), history of myocardial infarction ($X^2 = 6.071$; $P < .05$), and heart failure ($X^2 = 10.693$; $P << .05$) in patients infected with both Gram-positive and Gram-negative organisms.

Post hoc analysis was also done for the 539 of 560 patients by stratification into survivors ($N = 464$) and nonsurvivors ($N = 75$). Trough concentrations of 10.9 ± 5.9 and 7.8 ± 5.2 were noted for nonsurvivors and survivors, respectively. Students' t -test noted high troughs in nonsurvivors ($T = 4.090$; $P << .05$), perhaps reflecting organ failure. The log time to negative culture was 6.9 ± 2.9 and 4.2 ± 3.0 days for nonsurvivors and survivors, respectively ($T = 3.102$; $P = .002$), which was not surprising. A total of 51 of 75 patients were being treated with vancomycin at their demise again reflecting non-Gram-positive infection causes for nonsurvival. Log days of vancomycin therapy did not differ between nonsurvivors and survivors ($T = 0.868$; $P >> .05$). Normalization of white blood cell counts were 7.4 ± 2.5 and 4.9 ± 2.9 days ($T = 3.235$; $P = .001$) for the nonsurvivors and survivors, respectively. Log days to a heart rate < 91 beats/min was 8.5 ± 2.7 and 6.2 ± 3.3 days ($T = 2.311$; $P = .02$) for nonsurvivors and survivors, respectively. Smoking and ethanol abuse did not differ between survivors and nonsurvivors by

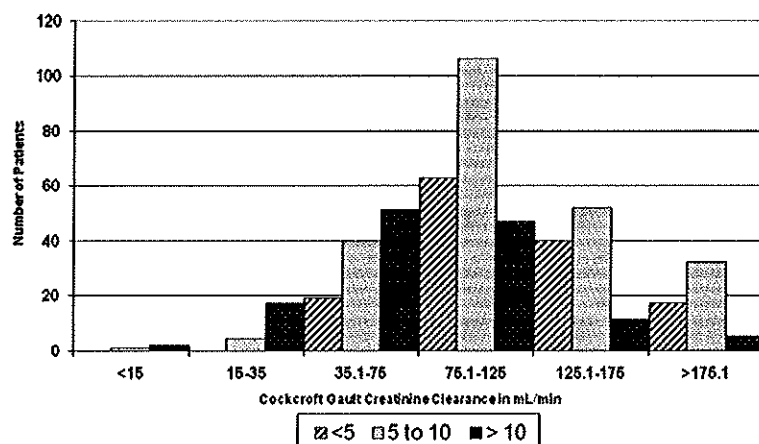


Figure 2. Distribution of creatinine clearance for the troughs <5, 5–10, and >10 mg/L.

χ^2 analysis. For nonsurvivors, a greater proportion had inhalation injury ($\chi^2 = 7.063$; $P = .007$), which was not surprising. Underlying cardiovascular disease also plagued the nonsurvivors with hypertension ($\chi^2 = 9.035$; $P < .05$), history of myocardial infarction ($\chi^2 = 18.393$; $P < .05$), and heart failure ($\chi^2 = 5.859$; $P = .01$).

DISCUSSION

If serum vancomycin trough concentrations were predictive of a more rapid resolution of signs and symptoms of infection, some difference should have been noted with a population of 560 patients. Instead, the patient trough concentration data was consistent with previously published in vitro time-kill data for both *S. aureus* and various coagulase negative *Staphylococcus* species demonstrating no difference in killing as vancomycin concentrations were

increased. These publications have noted unchanged killing rate in broth concentrations over a range of 5 to 50 mg/L.^{2,3,14,18-20,22} Duration of vancomycin therapy was unaffected by vancomycin trough concentrations when the >5 mg/L data were separately analyzed. In vitro testing via killing curves published 20 years ago also failed to demonstrate any increased killing rate with vancomycin broth concentrations >5 mg/L.^{2,3,14,18-20,22} Our vancomycin minimum inhibitory concentrations have remained <2 mg/L, and thus we may represent an atypical burn patient population that may not be universalized to one burn treatment center with higher vancomycin minimum inhibitory concentrations.

Resolution of signs and symptoms of infection likewise was not impacted by increased vancomycin trough concentrations above the 5 to 10 mg/L range. Stratification of patients based on their percentage BSA burn failed to demonstrate any measured benefit for increasing vancomycin trough concentrations beyond 5 to 10 mg/L. Delay in vancomycin response correlated poorly with trough concentration and could not be explained by any maldistribution of burn size among the strata.

Many of these patients (almost 1/2) had received a prolonged treatment course, or had repeated treatment courses of vancomycin. Serum creatinine >1.2 g/dL was noted in 77 patients, nephrotoxicity occurred in 20 of these patients. For the 442 patients with serum creatinines <1.2, only 15 of the 62 patients developed nephrotoxicity, whereas for the 118 patients with serum creatinine >1.2, 47 developed nephrotoxicity. Total days of therapy between the two groups were not statistically significant. The single-most prediction of vancomycin nephrotoxicity, as demonstrated in Figure 3, was the duration of vancomycin therapy as had been noted by Lodise et al.^{14,23-26}

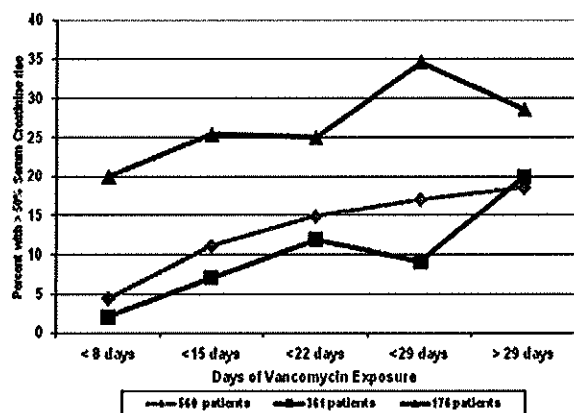


Figure 3. Percentage of patients demonstrating a >50% increase in serum creatinine as vancomycin therapy exceeded 8 days for the 361 trough patients and 189 patients with concomitant Gram-negative bacillary infections.

Patients with renal impairment did not differ with regard to duration of vancomycin therapy, time to resolution of signs of infection, nor in initial vancomycin trough concentrations when compared with the other strata. Patients with creatinine clearances <50 ml/min were more likely to be changed to linezolid during the course of vancomycin treatment. In Figure 3, a nearly parallel rise in renal impairment can be seen for the 361 patients under study and 189 patients with Gram-negative infections. For both patient populations a clear relationship between duration of therapy and increased percent of patients with a 50% serum creatinine rise can be seen as therapy exceeded 2 weeks.

It is the opinion of some clinicians that persisting fever and other signs and symptoms of infection for >5 days of therapy constitutes a vancomycin treatment failure. Using this criterion, the majority of our patients would have been vancomycin treatment failures. The marked disparity between actual treatment failure and five-day criteria treatment failure is of concern because it markedly differs from the actual response.

Stratification of patients by survival status failed to demonstrate a difference in trough concentrations between the two groups. Comparison of 75 patients with nearly 500 for the parameters chosen for this study demonstrated marked differences in response. Comparison of log-transformed data demonstrated that the nonsurvivors were sicker and more symptomatic of infection than survivors. These nonsurvivors had a greater proportion of inhalation injury and had a greater number of patients with underlying cardiovascular disease.

This study was limited by retrospective analysis of only 605 treatment courses in 560 patients. Removal of the *S. aureus* pneumonias because the data had been previously published removed another population of sick patients from analysis. These methicillin-resistant *S. aureus* pneumonia patients also failed to demonstrate a relationship between vancomycin trough concentrations and resolution of their pneumonia. Using the same trough concentration strata no difference in days to negative cultures, resolution of fever, resolution of tachycardia (heart rate < 91), or resolution of abnormal white blood cell counts could be associated with trough concentrations >10 mg/L ($F < 1.0$; $P > .05$) and resulted in this current investigation.

The definition of treatment failure as 5 days of continued symptoms in spite of vancomycin therapy is worrisome and, unfortunately, commonly quoted. Following this criterion, we would have converted 72% of our patients to another antimicrobial agent. Using our crude definition of treatment failure as

discontinuation of vancomycin in favor of linezolid, we noted failure in only 7% of our patients, meaning that vancomycin therapy was apparently successful in 93% of the treated patients. Given the caveats, if a large number of small burns and the low minimum inhibitory concentrations reported in our organisms, it seems that vancomycin trough goals of >10 and >20 mg/L did not impact treatment duration.

The use of log-transformed data instead of non-parametric tests of the untransformed data may have provided statistical significance where there was no significance, and likewise, may have failed to recognize statistical differences. This study should be undertaken at a larger burn treatment center with more extensive data on vancomycin than is available at our institution to further clarify this issue.

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Abstract

INTRODUCTION: Fungal infections are reported in approximately 11 to 17% of thermal injury patients. The most common infections involve *Candida* species and *Aspergillus* species infection, thus routine treatment of fungal infections often includes either fluconazole or an echinocandin when *Aspergillus* sp. is suspected.

CASE: A 50 year old male suffered a steam boiler explosion in an enclosed space. The patient was intubated and transferred to our burn treatment center with an estimated total body surface area flame injury of 64% with inhalation injury and confirmed C-3 to C-6 spinal column stenosis. The patient was hemodynamically stable with ventilatory support. Following consensus fluid resuscitation, the patient eventually developed a positive sputum culture with *Escherichia coli* and nasal cultures with *Staphylococcus aureus*. The patient was taken to surgery for excision and grafting on post burn day (PBD) 3 and following surgery a chest x-ray revealed a right upper lobe consolidation and new *Acinetobacter baumannii* isolate. On PBD 15, bronchoscopy with bronchoalveolar lavage revealed *A. baumannii*, *Klebsiella pneumoniae*, *Aspergillus fumigatus* and *Verticillum species*. On PBD 23, a sudden neurological change was noted with areflexia and flaccid paralysis and magnetic resonance imaging of the brain revealed 13 ring enhancing lesions consistent with multiple brain abscesses. On PBD 33, an echocardiogram demonstrated a patent foramen ovale. The patient was taken to the operating room for brain biopsy and abscess drainage. Cultures isolated *S. aureus* and *Scediosporium apiospermum* warranting a change to voriconazole. Three weeks after initiation of voriconazole, a CT scan of the brain revealed no further lesions and resolution of edema in the ring enhancing lesions. On repeat CT scan 8 days later regression was noted in the lesions.

CONCLUSION: Initial fungal therapy was selected presuming that the *A. fumigatus* in the lung was the causative organism in the brain abscesses. The worsening clinical course while being treated with caspofungin warranted brain abscess drainage and culture which revealed a fungal organism inherently resistant to caspofungin.

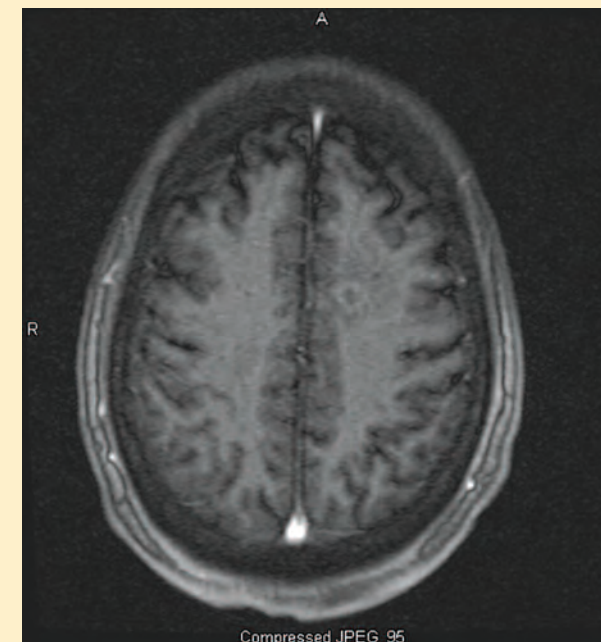
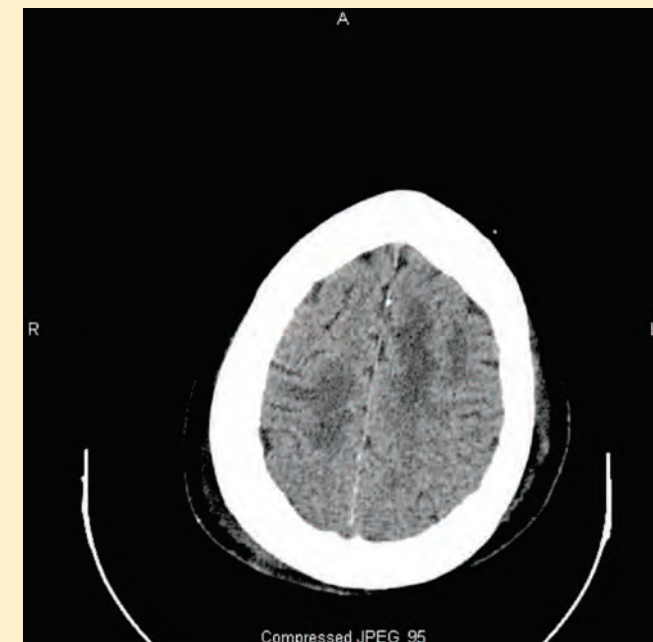
INTRODUCTION

Pseudallescheria boydii is a dimorphic fungus with its haploid form named *Scedosporium apiospermum*. It is isolated from soil, contaminated water, and manure and most commonly causes subcutaneous infection (mycetoma) of the lower extremities. CNS infection has been reported since 1953 with 25 published case reports. CNS infection is associated with sinus infection, immunosuppression, near drowning, or trauma. We report here a CNS infection in an immunocompetent patient following burn injury from a boiler explosion.

CASE REPORT

SR is a 50 year old male suffering a 64% total body surface area burn from an explosion in an enclosed space. Acute management of the patient over the next 48 hours included intubation, ventilator support, fluid resuscitation and bronchoscopy to assess the extent of inhalation injury.

Initial sputum isolates were *Escherichia coli* and *Staphylococcus* species for which cefazolin was empirically begun. The patient was taken on postburn day (PBD) 3 for excision and grafting of bilateral UE wounds. Chest x-ray on PBD 3 revealed a right lower lobe consolidation which was noted over the next 8 days. On PBD 10 the patient was taken again for excision and grafting. On PBD 11 *Acinetobacter baumannii* was isolated from the blood and Imipenem-cilistatin was begun. On PBD 16 bronchoalveolar lavage cultures (BAL) were obtained after follow-up bronchoscopy that yielded *A. baumannii*, *K. pneumoniae*, *Aspergillus fumigatus* and *Verticillum* species for which voriconazole was begun due to frequent isolation of *Fusarium* species in our burn treatment center. Chest x-ray on this day noted worsening infiltrates now also involving the right upper lobe. On PBD 35 an echocardiogram noted a patent foremen ovale as an incidental finding. On PBD 36 while antibiotics were being discontinued, the patient suddenly presented with flaccid paralysis and new neurological findings warranting a CT-scan.



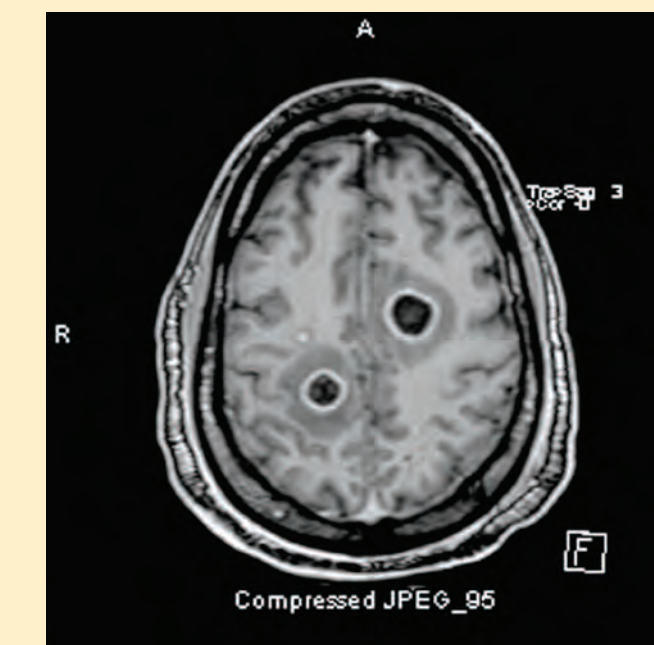
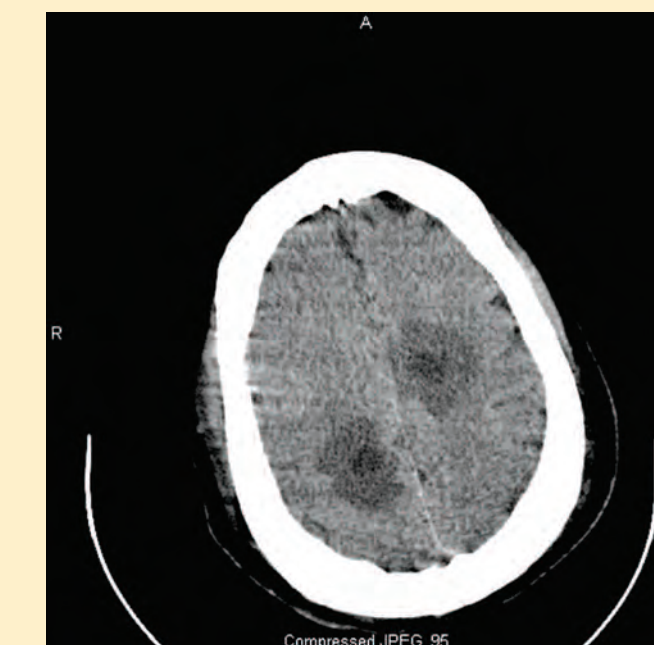
As can be seen in the Image above, approximately 13 ring enhancing lesions with vasogenic edema consistent with brain abscesses were noted. Due to the unstable condition of the patient, incision and drainage of abscesses was delayed for 7 days with empiric caspofungin directed at suspected *A. fumigatus*. On PBD 41 drainage of the abscesses and culture was obtained and reported later as *Staphylococcus aureus* and *P. boydii*. On PBD 47 an EEG was performed and was unremarkable with the exception of excessive theta waves. An MRI of the brain on PBD 49 demonstrated no change in lesions or midline shift. On PBD 62 a repeat CT scan of the brain revealed no further lesions and some resolution of edema; however there was now a midline shift.

CASE REPORT (continued)

On PBD 68 the patient was taken to surgery for excision of thick polyploid tissue noted on CT-scan. Culture of drainage noted no specific fungal or bacterial organisms. On PBD 71 a repeat MRI demonstrated reduction in the ring enhanced lesions and MRI on PBD 94 noted absorption of some of the abscesses. Sputum cultures on this day noted persistence of *A. baumannii* and *Pseudomonas aeruginosa*. Chest x-rays on PBD 98 and 100 were "grossly clear" and sputum cultures were now negative. On PBD 110 the patient was stable and transferred to a rehabilitation facility with follow-up in our outpatient burn treatment center. The patient was continued on oral voriconazole for a year and was readmitted for regrafting 223 days post discharge.

LITERATURE REVIEW

The most common fungal infections in burn patients is *Candida* species and *Aspergillus* species. Rare infections have been reported with *Fusarium* species. *Rhizomucor* species, *Penicillium* species and other "black molds" associated with agriculture and water damage to buildings. *P. boydii* is uncommon but can not be distinguished from *Aspergillus* species in histopathological specimens. Both can form "fungus balls" in the lungs or sinuses; however, *P. boydii* is resistant to many of the agents used against *Aspergillus* species. Treatment required surgical management followed by amphotericin B with a treatment failure rate of 50%. Susceptibility data for amphotericin B demonstrates a geometric mean MIC of 6.21 mg/L while voriconazole's is 0.73mg/L. The role of fungal sinusitis preceding pneumonia and other disseminated infections has been described and the association of near drowning with CNS infection warrants concern for occult fungal sinusitis precipitating disseminated fungal infections.



DISCUSSION

In our practice we commonly note *Scedosporium apiospermum* organisms in subsequent pneumonias. *Candida* and eosinophilic chronic rhinosinusitis can also be associated with CNS infection. The pulmonary and sinus infections are often disseminated. The multiple fungal isolations in this case suggest a disseminated infection. Findings in fungal sinusitis and may represent a hazard progressing to infection.

The patent foramen ovale is an asymptomatic finding in 25% of adults; however, it predisposes to dissemination of organisms to the CNS. Use of voriconazole is associated with a 50% success rate in approximately 50% of treated cases. The patient in this case was noted on multiple follow-up CT scans and a repeat MRI the next year demonstrated successful resolution of the abscesses. The importance of determining the presence of a patent foramen ovale and drainage was imperative for this case as the patent foramen ovale species alone had been isolated from the blood. Ineffective therapy with an echinocandin may have had a worse outcome.

Trimethoprim-Induced Hyperkalemia in Burn Patients Treated With Intravenous or Oral Trimethoprim Sulfamethoxazole for Methicillin-Resistant *Staphylococcus aureus* and Other Infections: Nature or Nurture?

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Trimethoprim is well known to cause rashes; however, what is not commonly known is that it causes sudden and profound hyperkalemia in 10 to 20% of treated patients. The uniqueness of burn patients begs the question whether changes known to occur in these patients might also increase this trimethoprim effect. After institutional review board approval, a retrospective study evaluated 224 patients with thermal injury who had been treated with trimethoprim sulfamethoxazole (TMP-SMX), 24 of whom had underlying renal impairment (creatinine clearances <50 ml/min) and were excluded, leaving 200 patients for analysis. Three definitions of drug-induced hyperkalemia were used: 1) a ≥ 1 mEq/L rise, 2) a >0.8 mEq rise in potassium in <24 hours warranting early discontinuation of TMP-SMX, and 3) "marked" hyperkalemia defined as serum potassium of ≥ 5.5 mEq/L within 48 hours. A potassium level before trimethoprim exposure (TxK) and after TxK were collected retrospectively. Demographic data were analyzed with Student's *t*-test and trimethoprim dose alone, demonstrating a significant difference. Analysis of 200 patients exposed to trimethoprim demonstrated an elevation of potassium (first definition) in 31 patients (15.5%), a rapid change in serum potassium in two patients (second definition), and marked hyperkalemia (>5.5 mEq/L) in 13 patients (6.5%). Hyperkalemia never occurred in 166 of 200 patients (82%; before TxK, 3.9 ± 0.4 ; after TxK, 4.3 ± 0.5 mEq/L). Change in serum potassium among patients with hyperkalemia was 4.0 ± 0.5 mEq/L before TxK and 5.3 ± 0.7 mEq/L after TxK. Twelve published hyperkalemia risk factors were reviewed in these 200 patients and only history of hypertension and need for intubation was more common in those with hyperkalemia. A nearly 20% incidence of hyperkalemia and 6% serious hyperkalemia in burn patients is consistent with reports in patients without burn injury. These data also suggest that the metabolic and hormonal changes associated with burn injury do not increase further the genetically predisposed hyperkalemia resulting from exposure to trimethoprim. These data suggest patients treated with TMP-SMX should have routine serum potassium monitoring before discharge. (J Burn Care Res 2013;34:127-132)

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For many patients with small burn injuries and patients with residual wounds at discharge, oral antibiotics often are sought to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA).¹ Staphylococcal infection represents one of the more serious graft-destroying organisms encountered in thermal injury,² and the rampant spread of community-acquired MRSA outside of the hospital remains

one of the risks in discharging patients with open wounds. The association of bacterial burden to wound healing has been well described and warrants the recommendation to treat patients with infected open wounds with oral antibiotics after discharge. No benefit of prophylactic antibiotic therapy for burn wounds has been demonstrated; however, persisting, untreated bacterial infection impairs wound reepithelialization.

There are limited available oral antibiotics with sufficient activity against *Staphylococcus* species and in particular with activity against MRSA. Persisting open wounds with cellulitis warrant treatment for patients being discharged from burn centers. Available antibiotic agents are limited to linezolid and trimethoprim sulfamethoxazole (TMP-SMX) for hospital-acquired MRSA; erythromycin and clindamycin represent additional agents that can be used to treat erythromycin/clindamycin-sensitive MRSA that is often community-acquired MRSA. The ineffectiveness of clindamycin and erythromycin against hospital-acquired MRSA limits the potential use of these two antimicrobials, and the excessive cost of oral linezolid limits its use in patients without insurance or for whom their insurance denies coverage for linezolid.³ For many patients treated in burn centers, oral TMP-SMX represents the only reasonable treatment option for persisting open wounds with cellulitis. The medication is generic, cheap, and readily available without the need for special ordering by community pharmacists.

Commonly used drugs like TMP-SMX have long histories of use and often are dispensed with little regard for potential or actual side effects. Drug-induced adverse effects are unexpected findings and represent a common cause for hospital readmissions or emergency department visits. TMP-SMX is a well-known cause of skin rash and exfoliative rashes.⁴ Burn centers frequently admit patients with Stevens-Johnson syndrome and toxic epidermal necrolysis as a result of treatment with TMP-SMX and thus are acutely aware of this potential risk of therapy. Discharge education often includes a discussion of rash and discontinuation of the drug should a rash appear, but hyperkalemia is not discussed.⁴

The trimethoprim component of this antibiotic combination is reported to cause sudden and profound hyperkalemia in 10 to 20% of patients treated with this drug.⁵⁻¹² Most clinicians prescribing TMP-SMX are unaware of this adverse effect and do not specifically monitor for it in patients before and after discharge from a burn center.^{9,13} Likewise, for emergency department physicians and other clinicians prescribing TMP-SMX, warnings concerning symptoms

for hyperkalemia and monitoring for hyperkalemia before discharge are not done.¹⁴ In many busy community pharmacies, patients are only warned about the potential for skin rash.¹⁴ Pharmacokinetic and drug metabolism changes are associated with thermal injury and along with physiologic changes may affect trimethoprim disposition in thermal injury.^{15,16} Hormone and metabolic changes in thermal injury affect electrolyte homeostasis and thus may add to the changes induced by TMP-SMX.⁹

Thermal injury is well known to result in elevation of catecholamines, vasopressin, hydrocortisone, and aldosterone.^{14,17-19} Thermal injury induces inflammatory changes that increase the risk of deep vein thrombosis, fluid retention, and insulin resistance. With all these changes, does the risk of hyperkalemia increase or does the burn injury protect against the development of hyperkalemia in burn patients exposed to trimethoprim? TMP-SMX is commonly prescribed to patients with residual open wounds with assessment of the need to continue therapy at subsequent outpatient clinic visits. This retrospective study sought to determine whether the incidence of hyperkalemia in burn patients was comparable with that reported in other patient populations because of the common use of TMP-SMX in outpatient management of small open burn wounds.

METHODS

After institutional review board approval for a retrospective study, 236 patients who had been treated with TMP-SMX were identified. TMP-SMX had been used for infections with *Stenotrophomonas maltophilia* and for management of infected wounds either while in the hospital or as conversion to oral therapy for persisting infection in anticipation of discharge within 48 hours. In addition, infections with *S. maltophilia* treated with intravenous TMP-SMX also were included in the analysis. Between 1999 and 2010, approximately 4187 patients were admitted to our burn center and 224 patients (excluding patients with HIV receiving chronic prophylaxis) were treated with TMP-SMX at discharge, representing approximately 5% of admitted patients.

Pharmacy records for administration of TMP-SMX specifically for thermal injury were reviewed. Normally patients are treated with one double-strength TMP-SMX tablet every 12 hours; however, dose adjustment was made for elderly patients over 75 to single-strength tablets every 12 hours. To be screened for initial inclusion in this study, patients were required to have had a potassium level obtained

the day before initiation of TMP-SMX and a potassium level obtained 24 to 48 hours after initiation of TMP-SMX. From this initial screening of hundreds of patients, 236 patients exposed to trimethoprim with necessary serum potassium concentrations then were subjected to further inclusion and exclusion criteria to come up with a final study population.

Inclusion criteria included the treatment of the patient for at least 24 hours with TMP-SMX for indications other than *Pneumocystis jirovecii* prophylaxis and a creatinine clearance estimate >50 ml/min.²⁰ Exclusion criteria included patients chronically managed with TMP-SMX for chronic urinary tract infection, patients taking TMP-SMX for *P. jirovecii* prophylaxis,²⁰ patients with evidence of HIV-related renal dysfunction whether they recently had been exposed to TMP-SMX, angiotensin-converting enzyme inhibitors, verapamil, heparin infusions, or succinylcholine.²¹⁻²⁷ Patients with chronic renal insufficiency, those requiring peritoneal or hemodialysis, requiring >40 mg furosemide per day,²⁸ or with a calculated creatinine clearance of <50 ml/min also were excluded from study entry. Patients with no potassium level 24 hours before administration of TMP-SMX and no potassium levels obtained after initiation of TMP-SMX were excluded during the initial patient screening. There were no missing potassium determinations in the screened patients.

The manufacturer recommends dose adjustment at ≤ 30 ml/min; however, no patient with a calculated creatinine clearance <50 ml/min was included in the analysis to assure that change in potassium was due to trimethoprim exposure. When applying the inclusion and exclusion data to the identified sample, 24 patients were excluded, leaving 200 patients for analysis. Three definitions of drug-induced hyperkalemia from the literature were used: 1) a ≥ 1 mEq/L rise in serum potassium after exposure to trimethoprim, 2) a rise of >0.8 mEq of potassium in less than 24 hours after initiating therapy with trimethoprim, and 3) "marked" hyperkalemia representing a rise in serum potassium to ≥ 5.5 mEq/L after exposure to trimethoprim.⁷⁻¹¹ To compare potassium levels, a potassium level was collected from the daily laboratory tests before initiation of TMP-SMX treatment, which was designated as the serum potassium before trimethoprim exposure (TxK); a second level obtained within 48 hours of the start of TMP-SMX therapy, designated the during therapy serum potassium level (after TxK), were collected retrospectively.

Demographic data and serum potassium data were stored in an Excel spreadsheet, and descriptive statistics from this program were used to characterize

collected data. Mean and SDs were compared with the median and first and third quartile values. Normality of the distribution of collected parameters was assessed by difference of mean from median and calculation of skew and kurtosis. Means with SDs greater than 35% of the mean were subjected to log transformation because less than 66% of the sample would be enclosed in 2 SDs from the mean. Patients were stratified into two groups: those with drug-induced hyperkalemia and those with no change in potassium with TxK. These data then were analyzed using Student's *t*-test with an eye on the possibility of nonnormal distribution. Pair-wise data were analyzed with Student's *t*-test and categorical data using χ^2 , seeking significance at .05.

Initial analysis of demographic data were age, creatinine clearance, TBSA of burn, injury severity score, burn probability of survival score, alternate probability of survival score, ventilator days, length of stay, amount of trimethoprim (mg/kg), and survival. This analysis was done to determine whether any of these parameters would have any effect on or increase the incidence of hyperkalemia in the burn patient population.

RESULTS

Of the 236 patients identified, 5 patients with HIV infection and 7 patients with incomplete medical records were excluded from the analysis. For the remaining 224 patients, potassium serum concentrations were available, permitting analysis. Creatinine clearance was less than 50 ml/min in 24 of these patients, and to be sure that renal dysfunction would not be included in the analysis, this value, which is greater than the 30 ml/min limit set by the drug manufacturer, was used as our cutoff for inclusion in the study. A total of 200 patients met the criteria for inclusion in the study (Table 1). Descriptive statistics and *t*-test analysis comparing patients with and without hyperkalemia following trimethoprim failed to demonstrate a difference in age, creatinine clearance, TBSA of burn, length of stay, or the number of ventilator days. The daily dose of trimethoprim for patients with hyperkalemia was 4.6 mg/kg/day (intraquartile range, 4.0-7.0) vs 4.0 mg/kg/day (intraquartile range, 3.4-4.8) for patients without hyperkalemia ($t = 3.04$; $P < .05$).

Using the first definition of hyperkalemia, a 1 mEq/L rise in serum potassium at 24 to 48 hours after initiation of TMP-SMX, a total of 31 patients (15.5%) had drug-induced hyperkalemia. The second definition was a >0.8 mEq rise in potassium less than 24 hours after initiation of TMP-SMX,

Table 1. Demographics of evaluable patients

Patients	Age (yr)	Creatinine Clearance* (ml/min)	TBSA† (%)	ISS	Ventilated (Days)	LOS‡ (Days)	TMP dose (mg/kg)
With hyperkalemia (n = 34)							
Mean	44.6	106.3	18.9	13.1	32.7	41.6	6.2
SD	20.6	40.9	21.7	14.0	44.0	42.0	3.7
Without hyperkalemia (n = 166)							
Mean	42.0	107.2	11.7	8.4	20.0	18.8	7.5
SD	17.0	45.2	14.7	11.0	26.9	22.0	1.9
Test§	<i>t</i> = 1.011	<i>Z</i> = 0.20	<i>Z</i> = 1.10	<i>Z</i> = 2.08	<i>Z</i> = 100.00	<i>Z</i> = 3.01	<i>Z</i> = 2.50
<i>P</i>	NS	NS	NS	<.05	<.05	<.05	<.05

*Cockcroft-Gault calculated creatinine clearance with correction for body weight only.

†The percent TBSA involved based on Lund and Broder.

‡Patients are directly discharged from the burn center.

§ Indicates value was obtained from Student's *t*-test; *Z* indicates the *Z* normal distribution from the mean.

ISS, Injury Severity Score; LOS, length of stay; NS, not significantly different.

and this occurred in two additional patients, warranting early discontinuation of TMP-SMX in favor of linezolid therapy. The third definition was the appearance of marked hyperkalemia (serum potassium >5.5 mEq/L) after initiation of TMP-SMX, which occurred in 13 patients (6.5%), for whom discontinuation of TMP-SMX was required.⁷⁻¹¹ All patients demonstrating elevation of serum potassium after initiation of TMP-SMX were treated with alternative antibiotics, most commonly with linezolid. Linezolid cost was justified to payers because of the noted hyperkalemia with TMP-SMX.

For 166 patients (82%), hyperkalemia following exposure to trimethoprim was not observed (before TxK, 3.9 ± 0.4 mEq/L; after TxK, 4.3 ± 0.5 mEq/L). TMP-SMX therapy was continued with no other complications for short treatment courses before patients were seen in the outpatient burn wound care center. For 34 patients (15.5%), hyperkalemia was observed (4.0 ± 0.5 mEq/L before TxK; 5.3 ± 0.7 mEq/L after TxK), warranting discontinuation of TMP-SMX in favor of other therapy. Survival for patients without hyperkalemia was 97% and 94% for patients with hyperkalemia, again indicating no real difference between those patients who developed hyperkalemia and those patients who did not. Death in these patients was not due to hyperkalemia. Sex did not predict risk for hyperkalemia because sex did not differ between groups. For 12 risk factors for hyperkalemia reported in the literature, only the number of patients with a history of hypertension ($\chi^2 = 4.96$; $P = .03$) and the number of patients in need of intubation at admission ($\chi^2 = 4.77$; $P = .029$) was significantly different for the patients with hyperkalemia.⁵ A list of these 12 risk factors is provided in Table 1. Comparison of

initial analysis parameters using a *t*-test was not statistically significant except for trimethoprim dose ($P < .05$). Of the patients in the nonhyperkalemia and hyperkalemia groups, 25.9% (43/166) and 26% (9/34), respectively, were younger than 30 years of age. Of the patients without hyperkalemia, 17% (28/166) had creatinine clearance of <60 ml/min; no patients with hyperkalemia had <60 ml/min creatinine clearance. TBSA >20% occurred in 15% (25/166) and 35% (12/34) of the nonhyperkalemia and hyperkalemia patients, respectively.

DISCUSSION

A nearly 20% incidence of hyperkalemia 17% (28/166) 6% incidence of serious hyperkalemia in burn patients is consistent with the literature about patients without burn injury.⁵⁻¹¹ The underlying diseases predisposing to hyperkalemia did not differ between the two groups, with the exception of the history of hypertension and patients requiring intubation and ventilatory support, which were higher in the hyperkalemia group.⁹ Likewise, the metabolic derangements associated with burn injury did not increase the incidence of hyperkalemia when compared with patients without burn injury.¹⁹ The central question of this research was to determine whether thermal injury had any effect on the development of trimethoprim-induced hyperkalemia. Ten of the 12 factors predisposing to hyperkalemia had near identical incidence in both groups (Table 2).⁹ It was demonstrated that burn injury also was not a predisposing factor for the development of trimethoprim-induced hyperkalemia. The near identical incidence of hyperkalemia in burn patients when compared with other patient populations would

Table 2. Risk factors for hyperkalemia

Risk Factors for Hyperkalemia*	Patients With Risk Factors	Patients Without Risk Factors	χ^2	P
Tobacco	65 (13)	149 (25)	0.32	.57
Diabetes	46 (9)	177 (29)	0.26	.609
Hypertension	76 (19)	145 (19)	4.95	.025
Cardiovascular disease	22 (5)	194 (33)	0.44	.504
Heart failure	10 (1)	207 (37)	0.41	.522
Heparin use	132 (22)	82 (13)	0.02	.875
Chronic diuretic use	133 (4)	87 (31)	0.15	.518
Angiotensin-converting enzyme use	28 (5)	191 (30)	0.08	.772
HIV infection	5 (1)	219 (39)	0.02	.899
β -Blocker use	28 (7)	208 (28)	2.02	.11
Nonsteroidal anti-inflammatory drug use	59 (14)	158 (25)	1.82	.177
History of intubation	50 (14)	169 (24)	4.77	.029

*HIV was an exclusion criteria for this study, eliminating five patients from the analyses.

Values reflect the number of patients from the initially screened group of 236 patients before exclusion; 224 patients were selected from this group for inclusion in the study. Data in parentheses represent the number of patient with hyperkalemia.

suggest that the hyperkalemia seen with TxK is the result of a genetic predisposition rather than the burns themselves. Patients with thermal injury demonstrated equal incidence of trimethoprim-induced hyperkalemia, based on reports in the literature. The high incidence of hyperkalemia (~20%) would indicate that mild hyperkalemia is common in patients treated with trimethoprim, and the 6% incidence of marked hyperkalemia is higher than the incidence of rash reported in patients without HIV who are treated with TMP-SMX.^{5,12}

The mechanism for trimethoprim-induced hyperkalemia involves inhibition of sodium transfer across the cell membrane rather than effects on potassium channels or efflux pumps.¹⁴ Acting on apical cell sodium channels in genetically predisposed patients, trimethoprim limits the transfer of sodium ions from the cell and thus prevents the exchange of potassium for sodium ions. As such, trimethoprim inhibition of sodium excretion prevents sodium-potassium adenosine triphosphatase influx of potassium in cells, with resulting elevation of potassium in blood. Patients in whom trimethoprim binds to sodium carrier proteins associated with the sodium channels thus are predisposed to this trimethoprim adverse effect.⁵ History of trimethoprim-induced hyperkalemia will result in subsequent episodes of hyperkalemia with trimethoprim rechallenge. Patients presenting with trimethoprim-induced hyperkalemia were advised to avoid future exposure to TMP-SMX. Patients with a family history of trimethoprim-induced hyperkalemia should be monitored carefully for this potentially serious and life-threatening adverse effect.

Although a significant difference in trimethoprim exposure in milligrams per kilograms per day was

noted by *t*-test analysis, ranges in doses between the two groups noted no trend suggestive of a clinical difference in trimethoprim exposure. The literature, however, does support a dose relationship for hyperkalemia.^{5,10} The small size of our sample with hyperkalemia and the range in doses in both groups may have accidentally demonstrated significance that other studies have seen more clearly.

These data would suggest early initiation of oral TMP-SMX in patients about to be discharged with residual wounds is warranted to permit detection of early TMP-SMX-induced hyperkalemia. These data would also suggest that serum potassium should be monitored routinely before discharge to assure that hyperkalemia from initial doses has not occurred. Initiation of oral antibiotic therapy would be best 24 to 48 hours before discharge to be sure that hyperkalemia associated with trimethoprim use is determined prospectively. These data would also suggest that serum potassium should be obtained again during the first outpatient clinic visit to determine whether there is trimethoprim-induced hyperkalemia during the first week of therapy.

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Comparison of Serum Vancomycin (VAN) Peak and Trough Concentration-Based Pharmacokinetic Parameters (PK-P) Versus Those Derived Creatinine Clearance (CLCr) and Patient Weight



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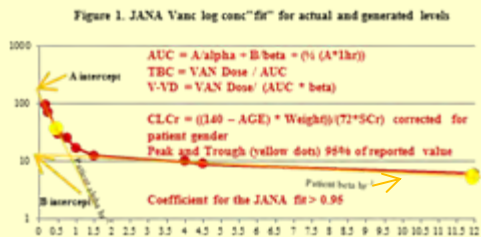
Introduction Vancomycin (VAN) remains an important antibiotic for the treatment of Gram positive infections including methicillin-resistant staphylococci.¹ Increasing VAN MICs reflect selection of staphylococci with thicker cell walls and may impact pharmacodynamics (PD).^{2,3} Current VAN trough goals presume higher area under the serum concentration time curve (AUC) to achieve this optimal killing.^{2,3} PD models however require a true receptor and a measurable response as drug concentration increases.^{2,4} Previously, higher VAN trough concentrations failed to predict efficacy and thus an AUC-based relationship was investigated.¹⁰

Materials and Methods As part of an IRB-approved retrospective study, 632 VAN peak-trough pairs from 225 patients were used to first estimate additional VAN concentrations (S-CONC) at 0.17, 0.25, 0.5, 0.785, 1.0, 1.5, 4 hours, and at the midpoint (see Figure 1) using previously published VAN rate constants¹¹ and the two compartment model equation with Cp time = peak * e^{-alpha * time} + trough * e^{-beta * time}.¹² Criteria for "usable" fits, CLCr estimations, and pharmacokinetic equations used are provided in figure 1.

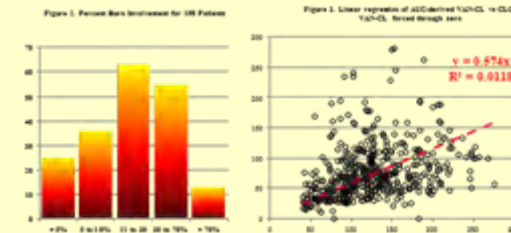
Patient data. Age, TBSA (see Figure 2), days of ventilatory support (VS), length of stay (LOS), days febrile (D-F), days with elevated white blood cells (D-W), days with elevated heart rate (D-T) and VAN treatment duration (D-VAN) were collected. Serum albumin (S-ALB) around the time of VAN sampling, increases in serum creatinine during VAN and at 10 days following VAN discontinuation were also collected.

Pharmacokinetic parameter (PK-P) analysis. Estimates for V-CL from CLCr were compared to AUC-derived data.^{2,12} CLCr was estimated using the Cockcroft-Gault equation using the adjusted body weight (see Figure 1).

PD analysis. Literature-based AUC goals were analyzed for LOS, survival, D-F, etc.



Statistical analysis. Median and 25% and 75% interquartile range (IQR) are reported. Data were stratified by survival status and 24 hour AUC (AUC < 400, 400 to 600, 600 to 800 and greater than 800). Linear regression of both V-CL estimates were done (See Figure 3). The four AUC strata were compared using analysis of variance (ANOVA) with additional assessment for normal distribution via skew and kurtosis and pair-wise comparisons for survival, etc., and used students t-test seeking an alpha < 0.05. To clarify the role the AUC plays in outcome, Analysis of Covariance (ANCOVA) was used.



Results
A total of 504 "usable" peak trough-pairs from 198 patients represented 79% of the original 632 sample. Table 1 below provides demographic data.

	CLCr	Age	%TBSA	LOS	Vent days	Mg/kg/day
All Patients (N= 198)	116 (78, 142)	42.5 (29, 53)	20.5 (7, 40)	24 (12, 47)	16 (8, 30)	27.8 (20.9, 34.5)
Survivors (N=143)	119 (82, 142)	41 (27, 54)	17 (6, 32)	21 (11, 41)	6 (0, 28)	26.2 (20.1, 30.9)
Survivors with CLCr > 60 (N= 140)	125 (97, 147)	37 (25, 48)	20 (6.6, 34.3)	19.5 (11, 40)	6 (0, 28)	26.2 (20.1, 30.9)

Inhalation injury (INH) was 63.5% for all patients. 60% of survivors, and 63% of survivors with CLCr > 60ml/min. VAN may have caused nephrotoxicity in 17 patients, but this toxicity did not correlate with age, TBSA, AUC 24, or D-VAN. Comparison of CLCr-derived² and AUC-derived VAN clearance resulted in the regression provided in Figure 3. The median 1kg V-YD was 0.58 (IQR 0.42 to 0.82) 1/kg for all patients, with a mean of 0.7 1/kg (consistent with the literature²) but with a wide standard deviation of 0.45 1/kg.

Results (continued)
ANOVA for the four strata of survivors are provided in Table 2. Larger AUC actually negatively impacted LOS, D-W, D-T and D-VAN. Larger 24 hour AUCs seemed to predict poorer response rather than an expected more rapid response to VAN. Though skew and kurtosis may have impacted comparison of D-F, D-W, and D-T, a large number of these patients (N = 80; 40%) had staphylococci in tracheal aspirate. Higher 24 hr AUCs did not increase resolution of symptoms, Vent days, D-VAN, nor LOS. Assessment of therapeutic response is often limited to Vent days, D-VAN, and LOS due to multifactorial causes of D-F, D-W, and D-T in thermal injury patients.

	%TBSA	V-S	LOS	D-F	D-W	D-T	D-VAN
Survivors (80)	F = 0.412	F = 0.628	F = 3.47	F = 2.56	F = 2.789	F = 3.65	F = 4.91
	NS	NS	P = 0.01*	NS	P = 0.04*	P = 0.01*	P = 0.002*

*P = Variance attributed to the larger AUCs contrary to expected better outcome with higher AUC

Skew and kurtosis did not explain the failure of higher 24 hr AUCs to positively impact LOS or D-VAN. ANCOVA verified that burn size did not influence resulting AUCs. ANCOVA demonstrated no bias with higher AUCs and D-VAN.

Discussion
VAN is dosed as mg/kg per day presuming a 0.7L/kg V-YD.¹² The wide variance in V-YD and V-CL^{2,13} warrants concern for the use of "standard" VAN dosing methods in burn center admissions,^{2,8,13} and is potentially fraught with error. Achieving higher 24 hr AUC goals does not improve VAN response defined as D-F, D-W, and most importantly with LOS, VENT or D-VAN.³ Perhaps this reflects the following wrong assumptions about VAN:

- 1) That VAN has a "receptor"¹⁸
- 2) VAN has concentration-dependent killing^{13,14}
- 3) That 24 hr AUC or VAN levels impact therapy.^{3,14}

Van treatment failure does not warrant increasing doses of VAN to achieve "better" P-D but selection of alternative agents.

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