Lean Six Sigma for Intravenous Therapy Optimization: A Hospital Use of Lean Thinking to Improve Occlusion Management

Lee Steere, RN, CRNI, VA-BC
Marc Rousseau, MBA, RPH
Lisa Durland, MS, RPH
Hartford Hospital, Hartford, CT

Abstract

Background: *Continual improvement is a necessary part of hospital culture. This occurs by identifying opportunities for improvement that influence efficiency while saving money.*

Methodology: *An investigation of intravenous device-related practices was performed by the nurses of the intravenous access team, pharmacy, and hospital operations at Hartford Hospital using Lean Six Sigma methodology. Central venous access device occlusion and tissue plasminogen activator variability was identified. Using observation, measurement of performance, and root cause analysis, the hospital's practices, policies, and equipment were evaluated for the process of occlusion management. The team utilized a Six Sigma strategy employing the elements define, measure, analyze, improve, and control, which is a disciplined, data-driven methodology that focuses on eliminating defects (waste). Interventions initiated based on the assessment performed by the team using the define, measure, analyze, improve, and control approach included replacement of negative displacement needleless connectors with antireflux needleless connectors and specialty team assessment before tissue plasminogen activator use.*

Results: *Over the course of the 26-month study, Hartford Hospital experienced a 69% total reduction in tissue plasminogen activator use representing a total 26-month savings of $107,315. Other cost savings were reflected in areas of flushing, flushing disposables, and in a decrease in needleless connector consumption. Central line-associated bloodstream rates fell 36% following the intervention as an unexpected secondary gain, resulting in further savings related to treating this nonreimbursable hospital-acquired condition.*

Conclusions: *This study examined the influence of using Lean Thinking and Six Sigma methodology as a tool in saving hospital money, resulting in better patient outcomes.*

Keywords: *central venous catheter, cost savings, lean six sigma*

Introduction

Among the most frequent complications associated with central venous access devices (CVADs) is catheter occlusion, ranging from 3%-79%.[1-4] Thrombotic formations on a CVAD are a natural physiological process in response to the insertion of foreign material into the body. Immediately upon insertion of an intravenous (IV) catheter, cells attach to the surface forming a fibrin coating.[5,6] This body response occurs soon after insertion and may develop around and within a catheter at any time during the IV treatment processes.[7,8] Intraluminal thrombotic catheter occlusion, a common noninfectious complication, is associated with negative outcomes of loss of patency (43%), device replacement (29%), device removal (14%), and hospital visits (15%) that all delay or disrupt the treatment process, slow a patient's progress toward therapeutic goals, and increase length of hospital stay and cost of care.[1,2,9,10]

Peripherally inserted central catheters (PICCs), a type of CVAD, have a higher incidence of occlusion than other chest-inserted central catheters potentially due to factors such as insertion into smaller peripheral veins, larger surface area, use of 3F-6F sizes with multiple lumens, and small catheter diameter.[2,11-16] Activities associated with PICCs for administration of IV medications and solutions require flushing, aspiration of blood, and connection and disconnection of needleless connectors (NCs) causing pressure changes within the catheter that result in venous blood cell deposits within the lumen of the

Correspondence concerning this article should be addressed to Lee.Steere@hhchealth.org.
https://doi.org/10.1016/j.java.2018.01.002
Copyright © 2018 Association for Vascular Access. Published by Elsevier Inc. All rights reserved.

catheter known as reflux. Reflux is associated with both mechanical and physiological pressure changes that force blood into the catheter lumen, leaving blood deposits contributing to the incidence of catheter occlusion.[17,18]

Reflux of blood into the terminal end of a catheter is a cause of catheter occlusion.[19] Patient movements, muscle flexing, and coughing all cause pressure changes and reflux within the catheter. As the catheter is manipulated, blood is intermittently pulled back into the catheter.[19,20] These deposits of blood on the catheter may be cleared, somewhat, with saline flushing.[21-23] When catheter lumen flushing is inadequate or blood protein deposits completely or partially block the terminal end of the catheter, these occlusions to the terminal end of the catheter may prevent blood sampling and the infusion of fluids.[10,21,24,25]

Lean Six Sigma

Hartford Hospital in Hartford, Connecticut, is an 867-bed regional referral center and the largest Hospital in the Hartford Health System. Lean Thinking and Six Sigma are 2 process improvement methods the IV Team at Hartford Hospital implemented to improve infusion therapy practices. The Lean Six Sigma (LSS) process is used to implement positive change by identifying inefficiencies, variables, process defects, and waste.[26-31] Specifically, LSS is a quality improvement methodology that originated during the 1970s with the Toyota Motor Company and Toyota Production System.[32] Much of the Toyota Production System way of thinking is based on the work of W. Edwards Deming.[33] Deming taught, among other things, that managers should stop depending on mass inspection to achieve quality, and instead focus on improving the production process, protocols, practices, and building quality into the product in the first place. LSS strives to pinpoint quality processes that correct identified defects in a system. Simply put, LSS means using less to do more.

The Lean Thinking concept was used initially in our department to improve the management of occluded CVADs. The hospital chose to study CVAD occlusion management while working to promote savings in medications, supplies, and time. This process allowed identification of variables that influenced the way occlusions were managed (ie, assessment of catheter function) and implement corrective actions that improved patient delivery of treatment without administering unnecessary medications.

The LSS data-driven quality method at Hartford Hospital was specifically guided by a programmed approach: defining, measuring, analyzing, improving, and controlling (DMAIC).[34-36]

The DMAIC phases:

- **Define** opportunity for improvement, project goals, and patient requirements.
- **Measure** pharmacy and medical supply consumption, overall cost, and performance.
- **Analyze** the consumption data to determine root causes of variation and poor performance (defects).
- **Improve** process performance by addressing and eliminating the root causes.
- **Control** by building a system of checks and adjustments for ongoing improvement in the process, protocols, practices, products, and patient outcomes (5Ps) of IV therapy.

The Hartford IV Team and stakeholders incorporated investigation of the 5Ps of IV therapy for insertion and management of vascular access devices. This process used the 5Ps as a tool to assist in differentiating value-added actions from nonvalue-added actions. By using the 5Ps systematic approach, waste and variability became obvious and detectable.

The LSS program at Hartford continued with agreement from the stakeholders from the supply chain and IV Team and from pharmacy, all committed to performance improvement. Infusion treatment with catheters in our facility represents more than 90% of our acute care hospital patients and CVADs are in use in approximately 50% of intensive care patients. Evaluating CVAD occlusion in terms of catheter function, flushing, and reflux had the potential to speed treatment and reduce occlusion complications. Wasted time, money, medical supplies, and pharmaceuticals and medications as well as logistics and nursing costs were all components because they applied to reported events of occlusion. LSS focuses on reducing defects, variability, and waste in current hospital IV access device practices.

Methods

The LSS methodology was used with the design indicated by the DMAIC process to define problems and goals, measure activities and supplies, analyze results, and devise improvement strategies based on analysis and control throughout the process. A team of clinicians trained in LSS evaluated procedures from October 2014 to December 2016 to identify problems, set goals to improve patient outcomes and reduce variability and waste resulting in long-term economic change. Goals and objectives for each patient outcome and the variability and waste sections were established for CVAD use, including heparin flushing, occlusion management, medication administration, CVAD replacement, and all associated supply costs.

DMAIC Phases

The LSS framework for infusion therapy practices at our facility began with a set of value-added actions and improvements identified through the DMAIC process. The DMAIC method was applied over 26 months as described in Tables 1–5. During the define phase (Table 1), products and patient outcomes were evaluated for IV therapy. A refined literature review delved into subjects of catheter patency; thrombotic occlusion; risks associated with tissue plasminogen activator (tPA) use; blood reflux; NCs; valves used in catheters and NCs; flush solution volume and frequency; and CVAD indications, appropriate use, and tip position.[10,17,20-22,37-51] The results of the literature review assisted in guiding the analysis process.[52,53] After defining key concepts and associated activities the process moved into the measurement phase.

The measure phase (Table 2) of DMAIC distinguishes specific goals that quantify practices and processes needing improvement. Measurement key areas included incidence of occlusion; drug use for occluded catheters; supply consumption

Table 1. Phase I: Define

1. Goals and objectives: Improve patient care, improve patient outcomes, reduce waste, reduce IV variability, and improve long-term economic results
2. Define and review IV therapy 5Ps (IV processes, IV protocols, IV practices, IV products, and IV patient outcomes)
3. Identify and target a specific hospital area (inpatient acute care areas) where peripherally inserted central catheter and central venous access devices are inserted and used
4. Focus on reducing pharmacy and medical supply waste by: a. Tissue plasminogen activator/tissue plasminogen activator use and associated cost, b. Flushing with heparin, c. Replacement and other costs associated with peripherally inserted central catheters and central venous access devices, and d. Reducing medical supply consumption and medical supply costs

IV = Intravenous.

specific to NCs; catheter volume and line days; and influence on central line-associated bloodstream infections (CLABSIs). NCs and add-on peripheral supplies were also evaluated and quantified. The NCs in use at our facility included a negative displacement valve (Clave; ICU Medical, Inc, San Clemente, CA). Collection of data, performed by the LSS clinicians and IV Team, established baseline levels for improvement, comparison, and analysis.

Table 2. Phase II: Measure[a]

1. Obtained alteplase/tissue plasminogen activator consumption data from pharmacy department
2. Obtained prefilled heparin flushing syringe consumption data
3. Reviewed alteplase/tissue plasminogen activator and heparin flushing 5Ps
4. IV Team began receiving daily tissue plasminogen activator consumption report from pharmacy department
5. Obtained central line-associated bloodstream infection rates since 2007
6. Obtained central line days since 2007 data
7. Obtained needleless connector consumption data

IV = Intravenous.
[a]We measured the 5Ps (IV processes, IV protocols, IV practices, IV products, and IV patient outcomes) against our defined goals and objectives to determine our current performance and quantify improvement opportunities.

Table 3. Phase III: Analysis[a]

Analyze all data collected and map potential performance opportunities
Review new needleless connector technology
Review literature regarding needleless connectors
Review infusion therapy evidence
Root cause analysis of tissue plasminogen activator use by registered nurses in intensive care unit
Registered nurses using tissue plasminogen activator without identifying cause of occlusion
Prioritize opportunities to improve

IV = Intravenous.
[a]Look for signs of IV waste, IV variability, and root causes of defects in our 5Ps.

In the analysis phase (Table 3), information obtained during the measure phase was mapped to demonstrate performance improvement opportunities as they applied to PICCs and all other CVADs. Root cause analysis of each occurrence of CVAD occlusion incorporated the 5Ps. Each identified occlusion event was accompanied by use of a thrombolytic medication (Cathflo; Genentech Laboratories, San Francisco, CA). Heparin and saline flushing practices, NC use, and associated supplies were included in the analysis. Understanding the outcomes of occlusion and subsequent complications led researchers to establish an implementation plan that resulted in improvement.

Table 4. Phase IV: Improve[a]

1. All nontunneled central venous access device catheters shall be effectively assessed by a trained and skilled IV Team RN for thrombotic occlusion before tissue plasminogen activator is ordered
2. Nontunneled Central Venous Access Device Patency Assessment Algorithm/Check List will be used to determine root cause of occlusions
3. IV Team will receive all orders from intensive care nurses so proper and effective assessments can be achieved by a trained and skilled IV Team RN
4. IV Team RN will order tissue plasminogen activator if appropriate
5. Eliminate prefilled maintenance heparin flushing with evidence-based outcomes
6. Implement use of Anti-Reflux NC to reduce unintentional blood reflux into peripherally inserted central catheter and central venous access devices and the associated risk of central line-associated bloodstream infection

VAT = Vascular access team.
[a]Improve processes, protocols, practices, and products to eliminate waste, variability, and defects to improve patient care and outcomes.

Table 5. Phase V: Control[a]

1. Nontunneled Central Venous Access Device Patency Assessment Algorithm/Check List continues to deliver the control necessary to sustain the tissue plasminogen activator use reduction, improvement in patient outcomes, and hospital economics
2. The antireflux needleless connector automatically provides blood reflux protection to sustain the heparin and corresponding tissue plasminogen activator use reductions that improve patient care and hospital economics
3. Unintentional blood reflux is controlled via use of antireflux needleless connector and the risk of infection and central line-associated bloodstream infection is reduced

[a]Control processes, protocols, practices, and products to eliminate waste, variability, and defects to improve patient care and outcomes.

The improve phase (Table 4) addressed the specific practice measures designed to meet the goals through the 5Ps. These measures included CVAD occlusion evaluation by the IV team before use of any thrombolytic medication. Compliance with flushing practices was measured as part of the processes instituted in the previous phase. Negative displacement NCs were replaced with antireflux NCs (Nexus Medical TKO-6P; Nexus Medical LLC, Lenexa, KS) designed to promote long-term patency.[47] Outcomes based on the antireflux NC change were reduced occlusion and NC supply consumption. Each of these improvement measures was projected to influence and reduce incidence of not only occlusion, but also CLABSIs, reduce delays in treatment of occluded catheters, and improve patient satisfaction by reducing anxiety associated with nonfunctional CVADs.

In the control phase (Table 5), processes were applied to all 5Ps to improve performance. The control process included implementing an electronic medical record ordering process for tPA that was hidden from view and application of an algorithm (Figure: Process Control for Occlusion Management) to evaluate all CVAD occlusions. Over the 26-month period, all stakeholders adopted these value-added actions and improvements to maximize care practices for patients with IV access devices at Hartford Hospital.

Results

The number of inpatient acute care patients with CVAD occlusions treated with tPA averaged 119 per month during 2014. Following implementation of an algorithm for appropriate use, IV Team assessment, and antireflux NCs, the hospital achieved a 56% reduction to a new average annual baseline of 53 occlusions per month for 2015. Further, the hospital achieved a 61% reduction in tPA use for occlusions to a new average annual baseline of 47 occlusions per month for 2016 (Table 6). The

Table 6. Baseline 2014 With Negative Displacement Connector Changing to Anti-Reflux Connector 2015-2016

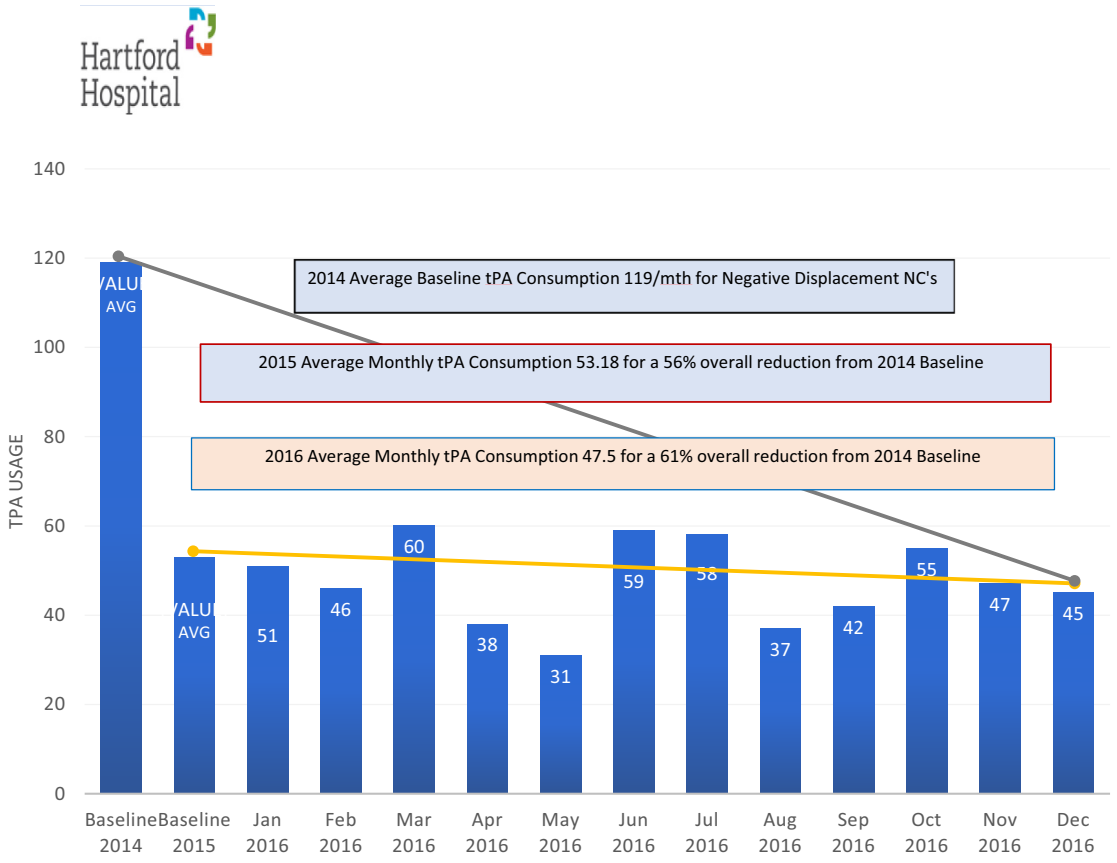


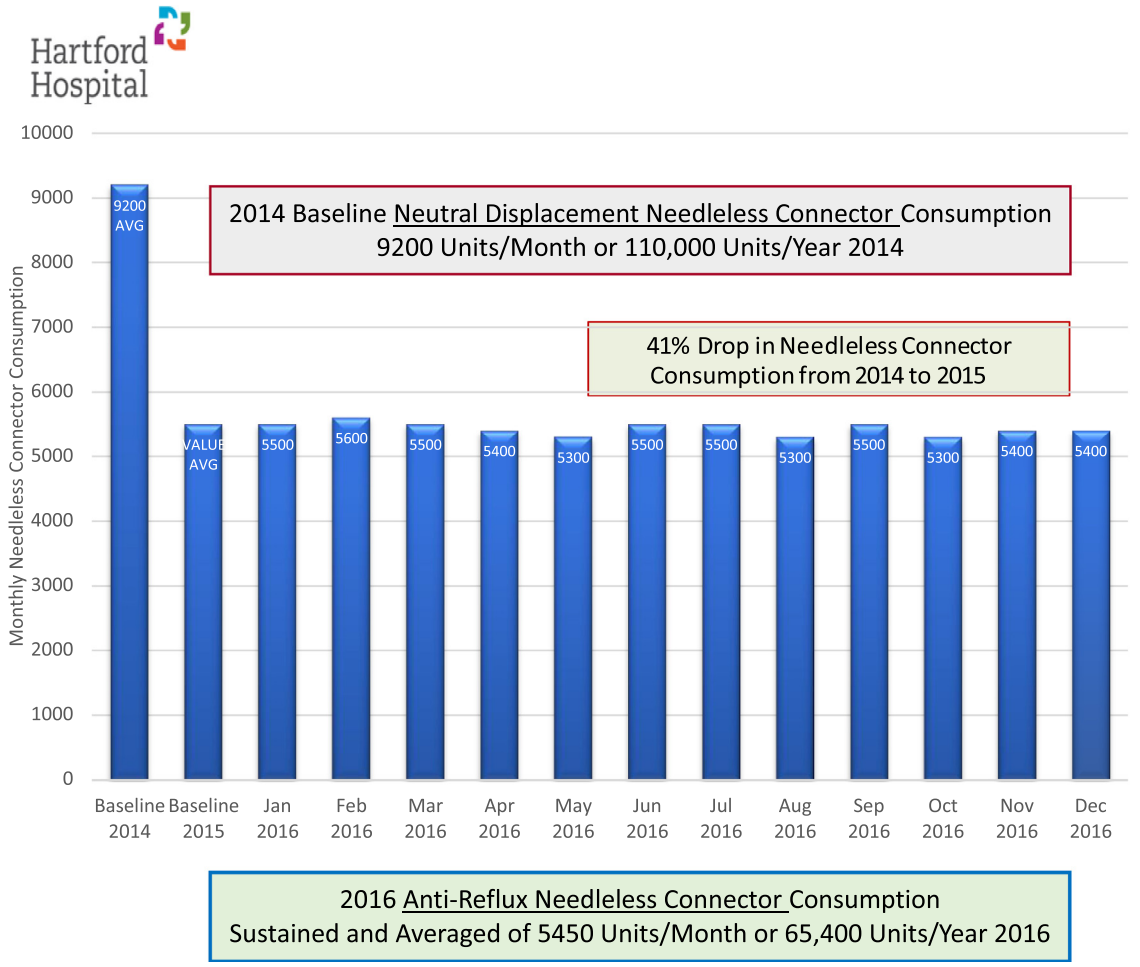
Figure. **Process flow for occlusion management.**

monthly range reflected a low of 31 occulusions per month to high of 60 occlusions per month. Decreased tPA consumption (at a cost of $65 per 1-mg dose) resulted in savings for 2015 of $51,480 per year and for 2016 of $55,835 per year. Over the course of the 26-month study, Hartford Hospital experienced a 69% total reduction in tPA use, representing a total 26-month savings of $107,315 (Table 6).

Following the intervention of new NCs there was a sustained medical supply reduction of 38%. The antireflux NCs showed a consumption reduction of 41%, which represented an annual decrease of 44,493 NCs. Costs associated with the previous negative displacement connector was $105,064 annually with a total consumption of 110,593 NCs. The replacement antireflux NCs cost $111,709 annually with a total consumption of 66,100 NCs (Table 7). The results of decreased occlusion, lower tPA use, and different NCs resulted in a positive annual savings of $100,670. Antireflux NCs have been validated for a full 7-day use, rather than the twice-a-week change associated with the NC our facility previously used. This resulted in less product use, less frequent CVAD line opening, and overall fewer catheter occlusions.

Flushing practices were reported from October 2014 through December 2016. Heparin flush use volume at baseline (2014) was 52,522 syringes at a cost of $0.55 per syringe. Heparin flush syringes were eliminated from the protocol while prefilled 10-mL saline flush syringes remain. The elimination of heparin flushing syringes resulted in savings of $28,887 annually.

Table 7. **tPA Usage Baseline 2014 with Negative Displacement Connector Changing to Anti-Reflux Connector 2015-2016**



In addition, the incidence of CLABSI as a secondary end point was evaluated. Retrospective data were combined with CLABSI results to reflect decreasing incidence from 2007 to 2016. Evaluation of the hospital intensive care unit CLABSI rate identified reductions from a 2007 calendar year high of 39 CLABSIs to a low of 9 CLABSIs in 2016. This change in CLABSIs represented a 77% decline over 9 years. Even more notable, the hospital's overall safety score fell from 0.475 to 0.301, a 36% reduction, well below the national average of 0.437.

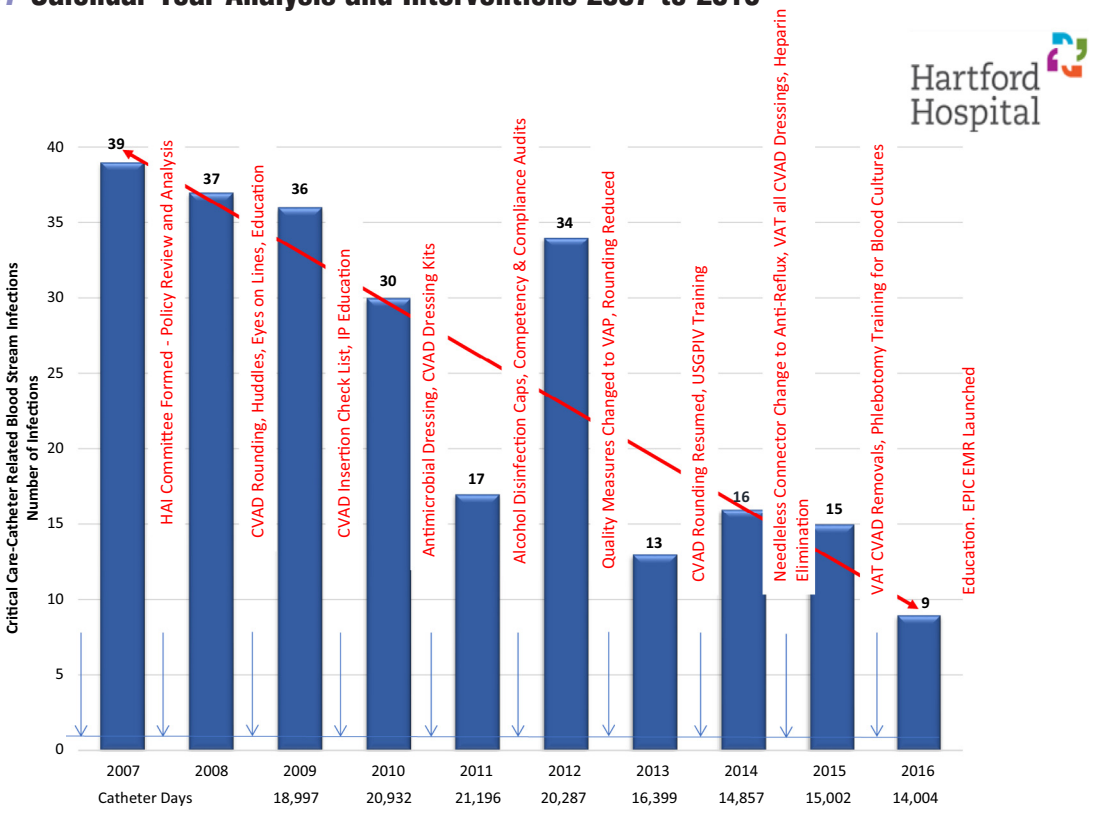
Discussion

Concerns over patient outcomes and the promotion of a culture of safety drove Hartford Hospital to examine processes, protocols, practices, and products along with outcome data collection. Ongoing patient and catheter complications resulted in catheter failure, including occlusion, phlebitis, and infection. These complications influenced function and efficacy in the delivery of treatment and thus were targeted by our facility's LSS health care initiative. The findings from the LSS DMAIC reflected areas of variability in CVAD occlusion management, NCs, flushing with heparin, and incidence of CLABSI.

Application of LSS identified specific components of the patient care process that were costly roadblocks to success. Catheter failure influences the ability to deliver treatment without interruption[16,54]; negatively affects patient, clinical staff, and pharmacy staff; and results in economic loss for hospital administration. Controls, such as assessment of catheter and insertion sites by vascular access specialists; use of an algorithm to properly troubleshoot reported occlusions; instillation of tPA only after careful assessment by vascular access specialists; and ongoing education of clinical staff for productive flushing, application of infection prevention measures, and aseptic technique for device management all worked together to improve patient outcomes and reduce risk. Using a focused approach to process improvement by combining Lean Thinking and Six Sigma, Hartford Hospital achieved an increase in positive outcomes.

Improvement represented by this initiative was sustained reduction in CVAD occlusions and tPA use. Sustained improvement is supported by methods instituted by the IV Team. During this intervention the focus was on 3 key drivers: patient satisfaction, quality, and improvement. One measure of those drivers was the amount of tPA used during the prior 24 hours. The IV Team reviewed every dose of tPA given via performance of an abbreviated root cause analysis. The IV Team verified that the algorithm had been applied and if not, the Team investigated the deviation. Reasons for tPA administration was documented on a Pareto Chart (depicting the frequency with which certain events occur), which allows better analysis of certain areas needing improvement. The

Timeline 1. **Calendar Year Analysis and Interventions 2007 to 2016**



IV Team at Hartford Hospital continues to meet at 7:15 AM daily for a Lean huddle. Every idea generated by the staff of the IV Team is considered as a possible LSS project.

The NC change and heparin elimination have continued to result in reductions in CLABSI. CLABSI risk factors are multimodal, with risk at insertion and during management of CVADs. CLABSI reduction initiatives began at Hartford Hospital in 2007 with CVAD rounding, huddles, and an Eyes on CVADs campaign. Foundational principles of a central line bundle consistent with recommendations were applied through hospital education programs.[55-57] After instituting education from 2007-2012, concerns over NC contamination were expressed as potentially occurring during flushing practices, resulting in NC colonization. Alcohol disinfection caps have been in use since 2010, including compliance audits, but CLABSI rates spiked in 2012. Occlusion in conjunction with blood reflux and NCs had not been considered as a risk factor despite the connection between thrombotic occlusion and infection.[58,59] In 1 study,[41] the relative risk of CLABSI associated with tPA use was 3 times that of patients who did not receive tPA. Although there were variables and limitations within the study period, the results suggest that the subsequent change to antireflux NCs and limited tPA use resulted in CLABSI reduction to a low of 9 infections in the critical care unit for 2016. Continued research is needed to completely evaluate the influence of reflux and tPA on infection risk within CVADs.

Hartford Hospital transitioned into a new electronic medical record system during August 2016. With this transition, there was a temporary reduction in data input and control over tPA use monitoring. This major change in hospital computer systems influenced the protocol and ordering process for tPA. There was concern that our tPA use would rise, but initiatives hardwired during the LSS phases were consistently maintained. No increase in tPA use resulted from the changes in the electronic medical record. The IV Team continued to directly monitor tPA use daily, focusing on why was it given, interventions performed prior, and who is ordering. Education of bedside nurses was instituted to improve practices that prevented occlusion. Education included training of productive flushing with a push pause action that creates turbulence and greater flush volume as needed. Bedside staff became accustomed to the new flushing practice and members of the IV Team evaluating catheter function before ordering of tPA. The bedside clinical staff has expressed appreciation for the IV Team efforts to help with troubleshooting occlusions, reducing medication administration delays and time spent with assessment, thus giving clinicians more time to focus on taking care of patients.

Limitations

This study has several limitations. First, the retrospective nature of the data collection for baseline results may reflect inaccuracies inherent in retrospective reviews. Measurement and tabulation of results were from methods that incorporated individual input, supply consumption data from material consumption and replacement of product, computer results of use within pharmacy distribution, and a period of years where computer upgrades and software changes may compound inaccuracies. Second, variables with multiple interventions in-

stituted and overlapping resulted in an inability to clearly indicate the intervention and its direct influence. A series of interventions initiated by the Healthcare Acquired Infection Committee occurred during the application of the LSS process. Variables were reduced during the final 2 years as the IV Team took more direct responsibility for interventions and activities of assessment, dressing changes, and complications management.

Conclusions

This Lean Thinking process with application of the Six Sigma DMAIC and 5Ps principles resulted in significant sustained improvement for our facility. Staff communication, goal setting, and application of a process established a staff culture that is continually striving for better outcomes. The steps for defining, measuring, analyzing, improving/implementing, and controlling the system identified areas of deficiency for CVAD occlusion management, flushing, and supply use. Reduced complications and cost savings provided value for the hospital. Of greater importance was the reduction of treatment delays and elimination of unnecessary medications and procedures.

Disclosure

Lee Steere is part of the Nexus Medical Speakers Bureau and has received honorarium for speaking engagements.

Acknowledgment

The authors thank Nexus Medical LLC (Lenexa, KS) and ICU Medical, Inc. (San Clemente, CA) for providing non-monetary project support and Nancy Moureau, RN, PhD, CRNI, CPUI, VA-BC for assisting with editing of the manuscript.

References

1. Ernst F, Chen E, Lipkin C, Tayama D, Amin A. Comparison of hospital length of stay, costs, and readmissions of alteplase versus catheter replacement among patients with occluded central venous catheters. *J Hosp Med*. 2014;9:490-496.
2. Moureau N, Poole S, Murdock M, Gray S, Semba C. Central venous catheters in home infusion care: outcomes analysis in 50,470 patients. *J Vasc Intervent Radiol*. 2002;13:1009-1016.
3. Walshe L, Malak S, Eagan J, Sepkowitz K. Complication rates among cancer patients with peripherally inserted central catheters. *J Clin Oncol*. 2002;20:3276-3781.
4. Wingerter L. Vascular access device thrombosis. *Clin J Oncol Nurs*. 2003;7:345-348.
5. Jacobs BR. Central venous catheter occlusion and thrombosis. *Crit Care Clin*. 2003;19:489-514.
6. Hardy G, Ball P. Clogbusting: time for a concerted approach to catheter occlusions? *Curr Opin Clin Nutr Metab Care*. 2005;8:277-283.
7. Stephens LC, Haire WD, Kotulak GD. Are clinical signs accurate indicators of the cause of central venous catheter occlusion? *JPEN J Parenter Enter Nutr*. 1995;19:75-79.
8. Hill J, Broadhurst D, Miller K, et al. Occlusion management guidelines for CVAD. *J Can Vasc Access Assoc*. 2013;7(suppl 1):1-34.
9. Gorski L, Perucca R, Hunter M. Central venous access devices: care, maintenance, and potential complications. In: Infusion Nursing: An Evidence-Based Approach. 3rd ed. St Louis, MO: Saunders/Elsevier; 2010:495-515.
10. Hadaway L. Major thrombotic and nonthrombotic complications. Loss of patency. *J Intraven Nurs*. 1998;21(suppl 5):S143-S160.
11. Valbousquet Schneider L, Duron S, Arnaud FX, et al. Evaluation of PICC complications in orthopedic inpatients with bone infection for long-term intravenous antibiotics therapy. *J Vasc Access*. 2015;16:299-308.
12. Hertzog D, Waybill P. Complications and controversies associated with peripherally inserted central catheters. *J Infus Nurs*. 2008;31:159-163.
13. Bartock L. An evidence-based systematic review of literature for the reduction of PICC line occlusions. *J Assoc Vasc Access*. 2010;15:58-63.
14. O'Brien J, Paquet F, Lindsay R, Valenti D. Insertion of PICCs with minimum number of lumens reduces complications and costs. *J Am Coll Radiol*. 2013;10:864-868.
15. Ullman A, Marsh N, Mihala G, Cooke M, Rickard C. Complications of central venous access devices: a systematic review. *Pediatrics*. 2015;136:e1331-e1344.
16. Smith S, Moureau N, Vaughn V, et al. Patterns and predictors of peripherally inserted central catheter occlusion: the 3P-O study. *J Vasc Intervent Radiol*. 2017;28:749-756.
17. Mayo DJ. Reflux in venous access devices: a manageable problem. *J Vasc Access Device*. 2001;6:39-40.
18. Chauhan A, Ghigo J-M, Beloin C. Study of in vivo catheter biofilm infections using pediatric central venous catheter implanted in rat. *Nature Protocol*. 2016;11:525-542.
19. Hadaway L, Richardson D. Needleless connectors: a primer on terminology. *J Infus Nurs*. 2010;33:22-31.
20. Elli S, Abbruzzese C, Cannizzo L, Lucchini A. In vitro evaluation of fluid reflux after flushing different types of needleless connectors. *J Vasc Access*. 2016;17:429-434.
21. Ferroni A, Gaudin F, Guiffant G, et al. Pulsative flushing as a strategy to prevent bacterial colonization of vascular access devices. *Med Device (Auckland, NZ)*. 2014;7:379-383.
22. Guiffant G, Durussel J, Merckx J, Flaud P, Vigier J, Mousset P. Flushing of intravascular access devices (IVADs)—efficacy of pulsed and continuous infusions. *J Vasc Access*. 2011;13:75-78.
23. Guiffant G, Durussel JJ, Flaud P, Vigier JP, Merckx J. Flushing ports of totally implantable venous access devices, and impact of the Huber point needle bevel orientation: experimental tests and numerical computation. *Med Device (Auckland, NZ)*. 2012;5:31-37.
24. Hadaway LC. Reopen the pipeline for I.V. therapy. *Nursing*. 2005;35:54-61, quiz, 61-53.
25. Hadaway LC. Prevent occlusions with these flushing pointers. *Nursing*. 2003;33:28.
26. Ahmed S, Manaf NH, Islam R. Effects of Lean Six Sigma application in healthcare services: a literature review. *Rev Environ Health*. 2013;28:189-194.

27. Pocha C. Lean Six Sigma in health care and the challenge of implementation of Six Sigma methodologies at a Veterans Affairs Medical Center. *Qual Manag Health Care*. 2010;19:312-318.
28. Pronovost P, Armstrong C, Demski R, et al. Creating a high-reliability health care system: improving performance on core processes of care at Johns Hopkins Medicine. *Acad Med*. 2015;90:165-172.
29. Daley AT. Pro: Lean Six Sigma revolutionizing health care of tomorrow. *Clin Leadersh Manag Rev*. 2006;20:E2.
30. de Koning H, Verver JP, van den Heuvel J, Bisgaard S, Does RJ. Lean Six Sigma in healthcare. *J Healthc Qual*. 2006;28:4-11.
31. DelliFraine JL, Langabeer JR 2nd, Nembhard IM. Assessing the evidence of Six Sigma and Lean in the health care industry. *Qual Manag Health Care*. 2010;19:211-225.
32. Evans JR, Lindsay WM. An Introduction to Six Sigma and Process Improvement. Boston, MA: Cengage Learning; 2014.
33. Bendell T, Penson R, Carr S. The quality gurus–their approaches described and considered. *Manag Serv Qual*. 1995;5:44-48.
34. Callahan CD, Roberts TS. Performance measurement and operations improvement using Lean Six Sigma. In: Practical Psychology in Medical Rehabilitation. New York, NY: Springer; 2017:569-573.
35. Shokri A, Shokri A. Quantitative analysis of Six Sigma, Lean and Lean Six Sigma research publications in last two decades. *Int J Qual Reliability Mgmt*. 2017;34:598-625.
36. Moraros J, Lemstra M, Nwankwo C. Lean interventions in healthcare: do they actually work? A systematic literature review. *Int J Qual Health Care*. 2016;28:150-165.
37. Bolton D. Preventing occlusion and restoring patency to central venous catheters. *Br J Community Nurs*. 2013;18:539-540.
38. Cummings-Winfield C, Mushani T. Restoring patency to central venous access devices. *Clin J Oncol Nurs*. 2008;12:925.
39. Gorski LA. Central venous access device occlusions: part 1: thrombotic causes and treatment. *Home Healthc Nurs*. 2003;21:115-121, quiz 122.
40. Hadaway L. Technology of flushing vascular access devices. *J Infus Nurs*. 2006;29:137-145.
41. Thakarar K, Collins M, Kwong L, Sulis C, Korn C, Bhadelia N. The role of tissue plasminogen activator use and systemic hypercoagulability in central line-associated bloodstream infections. *Am J Infect Control*. 2014;42:417-420.
42. Rupp M, Sholtz L, Jourdan D, et al. Outbreak of bloodstream infection temporally associated with the use of an intravascular needleless valve. *Clin Infect Dis*. 2007;44:1408-1414.
43. Khalidi N, Kovacevich DS, Papke-O'Donnell LF, Btaiche I. Impact of the positive pressure valve on vascular access device occlusions and bloodstream infections. *J Assoc Vasc Access*. 2009;14:84-91.
44. Ong CK, Venkatesh SK, Lau GB, Wang SC. Prospective randomized comparative evaluation of proximal valve polyurethane and distal valve silicone peripherally inserted central catheters. *J Vasc Interv Radiol*. 2010;21:1191-1196.
45. Hull G, Moureau N, Sengupta S. Quantitative assessment of reflux in commercially available needleless IV connectors. *J Vasc Access*. 2017, Dec 4:0. DOI:10.5301/jva.5000781.
46. Jacobs B, Schilling S, Doellman D, Hutchinson N, Rickeym M, Nelson S. Central venous catheter occlusion: a prospective, controlled trial examining the impact of a positive-pressure valve device. *JPEN J Parenter Enter Nutr*. 2004;28:113-118.
47. Jasinsky L, Wurster J. Occlusion reduction and heparin elimination trial using an antireflux device on peripheral and central venous catheters. *J Infus Nurs*. 2009;32:33-39.
48. Chopra V, Flanders S, Saint S, et al. The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC): results from a multispecialty panel using the RAND/UCLA Appropriateness Method. *Ann Intern Med*. 2015;163(6 suppl):S1-S40.
49. Moureau N, Chopra V. Indications for peripheral, midline and central catheters: summary of the MAGIC recommendations. *Br J Nurs*. 2016;25:S15-S24.
50. Jonker MA, Osterby KR, Vermeulen LC, Kleppin SM, Kudsk KA. Does low-dose heparin maintain central venous access device patency? A comparison of heparin versus saline during a period of heparin shortage. *JPEN J Parenter Enter Nutr*. 2010;34:444-449.
51. Hostetter R, Nakasawa N, Tompkins K, Hill B. Precision in central venous catheter tip placement: a review of the literature. *J Assoc Vasc Access*. 2010;15:112-125.
52. Steere L. Reduction in central venous catheter occlusions: impact of a pressure activated anti-reflux connector with a vascular access nurse algorithm in assessing occluded catheters. *J Assoc Vasc Access*. 2016;21:256-257.
53. Steere L. Examing the impact of proper central venous access tip placement in preventing occlusions. *J Assoc Vasc Access*. 2016;21:251.
54. Helm R, Klausner J, Klemperer J, Flint L, Huang E. Accepted but unacceptable: peripheral IV catheter failure. *J Infus Nurs*. 2015;38:189-203.
55. Marschall J, Mermel L, Fakih M, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:753-771.
56. O'Grady N, Alexander M, Burns L, et al. Centers for Disease Control and Prevention: guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52:e162-e193.
57. O'Grady D, Parmentier D, Woltman J. The journey to zero. *J Contin Educ Nurs*. 2012;43:199-200.
58. Raad II, Luna M, Khalil S-AM, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. *JAMA*. 1994;271:1014-1016.
59. Mehall J, Saltzman D, Jackson R, Smith S. Fibrin sheath enhances central venous catheter infection. *Crit Care Med*. 2002;30:908-912.