CLINICAL REPORT

Comparative risk of bloodstream infection in hospitalized patients receiving intravenous medication by open, point-of-care, or closed delivery systems

CATHERINE J. MERCALDI, STEPHAN LANES, AND JASON BRADT

Purpose. The impact of i.v. drug delivery via point-of-care (POC)-activated and closed systems versus traditional manual admixture systems on the risk of hospital-acquired bloodstream infection (BSI) is examined.

Methods. Using data from a proprietary hospital database, a retrospective observational cohort study of patients receiving one or more i.v. drug administrations via POC-activated or closed systems during a three-year period (2007–09) was conducted. Cases of hospital-acquired BSI were identified using diagnosis codes and billing charges for blood cultures and antibiotic use. The risk of BSI in patients with exposure to POC-activated systems, closed systems, or both relative to that of patients exposed to open systems was estimated by odds ratios (ORs) calculated by multivariate logistic regression analysis.

Results. The evaluated data indicated that of the 4,073,864 patients included in the study cohort, 0.5% (n = 20,251) experienced hospital-acquired BSI. After adjusting for selected confounding variables, the use of POC-activated systems was associated with a 16% reduction in BSI risk relative to the use of open systems (OR, 0.84; 95% confidence interval [CI], 0.76–0.93), and the use of closed systems correlated with a 12% risk reduction (OR, 0.88; 95% CI, 0.82–0.96). Patients who received i.v. drugs via both POC-activated and closed systems appeared to derive the greatest relative risk reduction benefit (OR, 0.12; 95% CI, 0.06–0.23).

Conclusion. Use of POC-activated and closed systems for i.v. drug delivery was associated with a significantly reduced risk of hospital-acquired BSI compared with exclusive use of open systems in a large population of hospitalized patients.

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Bloodstream infection (BSI) is a serious and preventable health outcome that accounts for over 1% of all hospitalizations in the United States and is associated with a fatality rate variously estimated at 20–50%.[1,2] The frequency of BSI has been increasing over the past several decades,[2] and prevention of nosocomial BSI due to contamination introduced within the hospital setting is a primary concern for health care officials.[3-5]

Intravenous administration of drugs and parenteral nutrition has been associated with an approximately 10-fold increase in the risk of nosocomial BSI among hospitalized patients.[1] Manual admixture of drugs and diluents in preparation for i.v. infusion has been identified as a potential source of contamination.[6] Manufactured closed drug-delivery modalities decrease the need for manual admixture and reduce the risk of contamination, thereby decreasing the risk of BSI associated with i.v. drug exposure.[7-9] In closed systems, also known as premixed or ready-to-use (RTU) systems, the drug and diluents are already mixed and packaged (possibly frozen and thawed to extend shelf life) in a bag ready for i.v. delivery.

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Delivery systems activated at the point of care (POC) allow drug admixture to occur at the time of administration; this is achieved by connecting a single-dose drug vial to a specially designed bag and then breaking the seal in the tube between the vial adaptor and the bag to allow the transfer of diluent into the vial, reconstituting the drug. The effect of POC-activated i.v. drug delivery on the risk of hospital-acquired BSI has not been well studied in the general population.

The objective of the study described below was to assess the impact of both POC-activated and closed i.v. drug delivery on the risk of hospital-acquired BSI in the general population. Because closed systems require the least manual manipulation, with the only human contact occurring when the health care provider connects the i.v. line, we expected that this i.v. delivery route would be associated with the lowest risk of hospital-acquired BSI. As POC-activated systems require the extra step of connecting the drug vial to the admixture bag, their use was expected to pose a slightly higher infection risk relative to the use of closed systems but less risk than that posed by traditional manual admixture (also known as "open") systems. We evaluated these hypotheses by conducting a retrospective cohort study using the Premier Perspective Comparative Database of U.S. inpatients (Premier Inc., Charlotte, NC).

Methods

Data source. The study was conducted using 2007–09 data from the Premier Perspective database, which includes claims data from more than 600 hospitals, with more than 5 million hospital discharges added annually. For these discharges, there are more than 5 billion daily service records, and about 65 million service records are added each month. The Premier data contain basic patient characteristics; *International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9)* and *Current Procedural Terminology, 4th Edition (CPT)* codes; and a date-stamped log of all billed items (including procedures, medications, and laboratory, diagnostic, and therapeutic services) at the individual patient level. Hospitals submitted data on a quarterly or monthly basis. The data underwent quality checks, and cost information was reconciled with the hospitals' financial statements.

Patient identification. The study cohort included all hospitalized patients (inpatient only) in the Premier database from January 1, 2007, to December 31, 2009, who received at least one parenteral administration of any drug available via POC-activated or closed administration (Appendix A). Because some hospital charge descriptions did not have adequate detail to allow a determination of i.v. delivery modality, only patients admitted to hospitals where POC-activated or closed systems could be identified were included in the study.

Any patient for whom there was documented evidence of BSI or another infection at the time of admission was excluded from the study. BSI or another infection at the time of hospital admission was assumed if the record contained either an admitting *ICD-9* diagnosis code (Appendix B) for infection or evidence of infection within 48 hours of admission (as determined by a combination of blood culture and i.v. antibiotic billing charges). If the date of BSI diagnosis could not be confirmed using data in the billing charges, the patient was excluded from the analysis. Thus, the study population included only patients for whom there was no evidence of infection at admission or within 48 hours after admission.

Patient characteristics. Baseline demographic and hospitalization characteristics were summarized on the basis of variables in the Premier database captured at the time of the hospitalization. Demographic variables included age at hospitalization, sex, race, geographic region, and primary payer. Hospitalization characteristics included hospital size, teaching hospital status, hospital location (urban or rural), year of admission, admitting diagnosis, type of admission, and transfer status.

Exposure definitions. Only i.v. drug exposures occurring prior to the BSI diagnosis date (as defined below) were considered as potential risk factors for patients who fit the criteria for having a hospital-acquired BSI event. Each charge for i.v. drugs examined (Appendix A) was categorized as associated with the use of an open, a POC-activated, or a closed i.v. delivery system. To classify each administration, we searched the hospital-provided charge descriptions for evidence of the use of POC-activated or closed systems. POC-activated systems included Mini-Bag Plus (Baxter Healthcare Corporation, Deerfield, IL) and ADD-Vantage System (Hospira, Inc., Lake Forest, IL) products. Closed administration systems included Duplex (B. Braun Medical Inc., Bethlehem, PA) frozen premix products, and RTU premix products. All other i.v. drug products were considered to have been administered via open systems. For each drug, up to 50 hospital charge descriptions were explored for key search terms in order to distinguish between the specified administration systems. The full set of categorized charge descriptions was then reviewed by a clinical expert, whose input was used to refine the search terms.

For each patient, we calculated the proportions of i.v. drug exposure resulting from the use of open, POC-activated, and closed systems by dividing the number of administrations in each category by the total number of administrations of the study drugs; the latter value was calculated by summing the quantity on

the applicable billing claims. Because virtually all patients had exposure to open systems, we used the median proportion of each i.v. administration type (i.e., open, POC-activated, closed) to divide the patients into high- and low-exposure categories. Due to the limited use of POC-activated and closed systems—the median proportion of use was zero for both—any exposure to these systems prompted the automatic assignment of patients to the applicable high-exposure categories. Thus, the final comparison groups for the study consisted of (1) patients with exposure to only open i.v. administration systems, who were referred to as the "Open Only" group, (2) patients with exposure to only POC-activated systems, dubbed the "POC-Activated (No Closed)" group, (3) patients with exposure to only closed systems, referred to as the "Closed (No POC)" group, and (4) patients with exposure to both POC-activated and closed systems, termed the "POC-Activated and Closed" group. The classification of patients with some exposure to open systems into the POC-Activated (No Closed) and Closed (No POC) groups was permitted, as long as at least one of their i.v. drug administrations was delivered via a POC-activated or closed system.

Several of the drugs offering both POC-activated and closed-system administration options were anti-infective medications. Because the use of i.v. antiinfectives could have reflected either the treatment of hospital-acquired BSI (the outcome of interest) or a non-BSI-related exposure unrelated to BSI (i.e., the treatment of an infection other than a BSI), these drugs were considered separately from other i.v. drugs. We also conducted a sensitivity analysis including only patients who did not receive i.v. antibiotics before BSI diagnosis (or, in the case of patients without BSI, did not receive any antibiotics).

Risk factors. We examined several factors shown to influence the risk of hospital-acquired BSI, including hospital length of stay (LOS), days in the intensive care unit (ICU), surgical patient status, central venous catheter (CVC) use, mechanical ventilator use, trauma patient status, hemodialysis, malnutrition, and other infections.[1] Hospital LOS and ICU days were calculated from billing claims for room and board charges, and surgery was inferred for patients with at least one billing charge from the surgery department. *ICD-9* and *CPT* codes for other risk factors are provided in Appendix B.

For patients with hospital-acquired BSI, we calculated risk factors using only prediagnosis information. For instance, only the LOS and days in the ICU before the diagnosis date were counted for patients with hospital-acquired BSI. Similarly, only data on surgery, CVC use, ventilator use, and hemodialysis prior to a diagnosis of hospital-acquired BSI were included in the risk factor analysis.

In addition to categorizing patients into analysis groups based on their relative exposures to various i.v. drug administrations, we created variables summarizing the absolute amount of i.v. exposure to be considered as risk factors. These included the total count of i.v. drugs administered per patient, both as a continuous variable and categorized into quartiles based on the distribution of the data. Values are provided for total exposure to the study drugs, as well as for antibiotic and nonantibiotic study drugs separately. We also quantified exposures to additional i.v. products, including items such as i.v. drugs not under study and parenteral nutrition and supplements. Additional i.v. exposures were identified from claims with a billing charge code containing the word "parenteral" in the product description.

Outcome ascertainment. Hospital-acquired BSI was defined using *ICD-9* diagnosis codes (Appendix B) in combination with billing charges for blood cultures and i.v. antibiotics. To limit the analysis to hospital-acquired BSI, patients whose case data contained evidence of infection within 48 hours of admission were excluded from the study, and we only included data on events occurring after the second inpatient service day.[10] Because *ICD-9* diagnosis codes in the Premier database are not linked to the day of diagnosis, an algorithm was devised to estimate the date of the BSI event. Specifically, if the patient had an *ICD-9* diagnosis code for BSI and a billing charge for a blood culture, then the service date of the blood culture charge was considered the diagnosis date. If a patient with BSI had multiple blood culture charges, then the service date of the first culture charge followed by an i.v. antibiotic charge within two days was considered the diagnosis date. If the patient had a BSI diagnosis but no blood culture charge was recorded, the first service date associated with a billing charge for i.v. antibiotic therapy was considered the diagnosis date.

Any patient whose BSI diagnosis date was on or before the second day of the hospital stay was considered to have been admitted with BSI and thus excluded from the analysis. Similarly, patients with an *ICD-9* diagnosis code for BSI but no subsequent blood culture or i.v. antibiotic charges were excluded because the diagnosis date was undefined (per the above definition) and we were thus unable to determine whether the infection was present on admission.

Analytical methods. Baseline demographic, comorbidity, and hospitalization characteristics were analyzed by i.v. drug exposure category using means with standard deviations and medians with ranges for continuous variables; raw counts with percentages were used for the analysis of categorical measures. For all comparative analyses, patients

in the Open Only exposure category were considered as the referent group. Unadjusted rates of BSI were computed, by exposure group, according to the group's risk (expressed as a risk ratio [RR] with a 95% confidence interval [CI]) relative to the Open Only group.

We used the odds ratios (ORs) obtained from multivariate logistic regression to estimate the risk of BSI in patients with at least one exposure to POC-activated or closed systems relative to patients who received drugs through open systems only, adjusting for potential confounders. Covariates included the stated demographic and hospitalization characteristics, as well as the examined risk factors for BSI (number and type of parenteral exposures, hospital and ICU LOS, surgery, trauma, CVC use, ventilator use, hemodialysis, malnutrition, and other infection). Continuous variables were categorized based on observed distributions. Each potential confounder was added individually to the logistic regression model of BSI and i.v. drug exposure. The final model included any covariate that modified the OR for BSI by at least 10% regardless of its statistical significance. Results of the final logistic regression models are presented as ORs with 95% CIs and *p* values; when the frequency of a given outcome is small (<10% of the population), the OR provides a good estimate of relative risk,[11] and that was the case in this study. Multivariate analyses were repeated for patients who did not receive i.v. antibiotics prior to or without a BSI event. All analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC), with the a priori level of significance set at 0.05.

Results

Using the 2007–09 Premier database, we identified just over 10 million hospitalized patients who received at least one i.v. drug. Nearly half these patients were excluded from our analysis on the basis of data indicating an admission to a hospital or other provider facility where the use of POC-activated or closed-system i.v. drug delivery products could not be identified (because these products were not used in the facility or charge-description details were insufficient to allow the classification of the i.v. drug exposure). After excluding patients with evidence of infection at or within 48 hours after admission (9.4%), the final cohort included 4,073,864 patients.

Among patients included in the study, 262,209 (6.4%) received i.v. drugs through closed systems (but not POC-activated systems), 99,149 (2.4%) received i.v. drugs via POC-activated systems (but not closed systems), and 5,053 (0.12%) received drugs using both POC-activated and closed systems; 3,707,453 (91.0%) received i.v. drug administrations only from open systems. The most common i.v. administrations regardless of type contained sodium chloride (68.2% of all patients), dextrose (41.8%), fentanyl (27.1%), midazolam (22.4%), cefazolin (19.6%), morphine (13.5%), or heparin (13.4%). Patients who received drugs via open systems exclusively had the lowest total i.v. exposures (both for drugs of interest and additional parenteral exposures), while patients receiving drugs delivered via both POC-activated and closed systems had the highest total exposures (Table 1). Among patients who received drugs via POC-activated or closed systems or both (i.e., non-open systems), about one third of all exposures to drugs of interest were administered via non-open systems. Antibiotic administrations accounted for much of the exposure to non-open systems in these groups (Table 1).

With regard to baseline demographic information, patients who received i.v. drugs only via open systems were younger, more likely to be female, less likely to be from the Midwestern region of the United States, and more likely to be on Medicaid than patients who received i.v. drugs via a combination of delivery systems (Table 2). Patients who received any POC-activated or closed-system drug products were more likely to have elective admissions (Table 2).

Patients with exposure to POC-activated and closed administration systems had a longer LOS, were more likely to be in the ICU, and had higher rates of all BSI risk factors, including surgery, trauma, CVC use, mechanical ventilation, hemodialysis, malnutrition, and other infections (Table 2).

We determined that BSI occurred in 20,251 (0.5%) of patients who received at least one i.v. exposure to a drug under study. Patients in the POC-Activated and Closed group, as well as those in the Closed (No POC) group, had a significantly reduced risk of BSI (risk reductions of 0.2% and 0.3%, respectively) compared with the Open Only group (0.5%); those risk reductions corresponded to unadjusted RR values of 0.39 (95% CI, 0.21–0.72) and 0.63 (95% CI, 0.59–0.67), respectively (Table 3). The unadjusted risk of BSI was similar in the POC-Activated (No Closed) and the Open Only groups. RRs for BSI were fairly consistent among patients receiving drugs in each of the examined classes.

After adjustment for selected confounding variables, both i.v. drug exposure via POC-activated systems and i.v. exposure via closed systems were associated with a significantly reduced risk of BSI compared with i.v. drug exposure exclusively via open systems (Table 3). Patients who received drugs via both POC-activated and closed systems had the lowest rate of hospital-acquired BSI, with an 88% reduction in odds (OR, 0.12; 95% CI, 0.06–0.23, $p < 0.0001$). Considered separately, the use of POC-activated systems alone and closed systems alone reduced the risk of hospital-acquired BSI by 16% and 12%, respectively.

A total of 2,153,321 patients (52.9% of the original cohort) had no exposure to i.v. antibiotics prior to BSI diagnosis or discharge and were included in the sensitivity analysis. Among these patients, having i.v. drug exposure from closed systems was associated with an 86% reduction in the risk of hospital-acquired BSI, and exposure to POC-activated systems was associated with a 49% risk reduction. None of the patients included in the sensitivity analysis had exposure to both types of systems during the hospitalization.

Table 1.
Drug Administrations Stratified by Exposure Category[a]

Exposure Category[b]	Mean No. I.V. Drug Administrations per Pt, by Type of Delivery System		
	Open	POC-Activated	Closed
All Drug Administrations			
Open Only	11.5	. . .[c]	. . .
POC-Activated and Closed	27.8	4.2	6.6
POC-Activated (No Closed)	14.2	7.3	. . .
Closed (No POC)	12.6	. . .	6.5
Nonantibiotic Administrations			
Open Only	9.3	. . .	. . .
POC-Activated and Closed	25.9	0.5	0.1
POC-Activated (No Closed)	14.0	0.6	. . .
Closed (No POC)	12.6	. . .	0.1
Antibiotic Administrations			
Open Only	2.8	. . .	. . .
POC-Activated and Closed	4.9	3.1	5.7
POC-Activated (No Closed)	2.5	5.5	. . .
Closed (No POC)	1.7	. . .	5.4
Additional Parenteral Exposure			
Open Only	8.7	. . .	. . .
POC-Activated and Closed	26.7	0.0[d]	0.0[d]
POC-Activated (No Closed)	11.4	0.0[d]	. . .
Closed (No POC)	13.5	. . .	0.0[d]

[a]POC = point of care.
[b]Patients in the POC-Activated and Closed, POC-Activated (No Closed), and Closed (No POC) categories were allowed exposures to open systems.
[c]Not applicable.
[d]Exposures occurred, but the mean number of administrations, when rounded, was 0.0.

Discussion

Nosocomial BSI is a serious and often preventable adverse event for hospitalized patients.[12,13] Simple solutions, including systematic hand washing and training programs in drug administration, are important first steps in reducing the risk of BSI.[1,13] New technologies that reduce the amount of manual manipulation required to administer i.v. solutions can provide additive reductions in BSI risk. In the large population of U.S. hospitalized patients receiving i.v. drugs that was evaluated in our study, the use of POC-activated and closed drug delivery systems was infrequent, with 90% of patients having exposure to only open systems. Even among patients with at least one exposure to a POC-activated or closed system, the proportion of all i.v. drugs administered via open systems averaged two thirds. The results of this study demonstrated that, conditional on total i.v. exposures, the increased use of closed and POC-activated i.v. drug delivery systems was associated with a significant reduction in the risk of hospital-acquired BSI.

These results are supportive of a growing body of literature. For patients with indwelling catheters for long-term medication delivery, closed-hub catheter systems have been shown to substantially reduce the risk of BSI.[7,8,14] More recently, closed infusion containers have been shown to reduce the risk of central line-associated BSI compared with open systems.[15-17] Similarly, patients receiving premixed parenteral nutrition solutions have been shown to have a substantially reduced risk of BSI relative to those receiving traditionally compounded parenteral nutrition.[18] Whether or not other delivery systems that limit manual admixture of drug and solution have a beneficial impact on BSI rates has not been extensively examined. A study of 300 infants did not find a BSI risk-reduction benefit with the use of a closed system of drug administration,[9] but these results may not be generalizable to adult populations. The study described here evaluated a diverse cross-section of U.S. hospitalized patients of all ages. Hospitals may wish to consider expanding the use of POC-activated and closed drug delivery systems in light of potential cost savings as well as patient safety benefits.

In our study, even though they were older and sicker at baseline by nearly all health-related measures (e.g., hospital LOS, ICU days, all additional BSI risk factors), patients receiving drugs via both POC-activated and closed systems, as well as those receiving closed-system administrations only, had lower rates of BSI than those receiving open-system administrations—even before adjusting for health status. Patients with exposure to both POC-activated and closed drug delivery systems derived the greatest risk-reduction benefit relative to patients with only open-system exposure (in this group, a larger proportion of administrations were given via closed versus

Table 2.
Baseline Demographic and Hospitalization Characteristics of Patients Receiving I.V. Drugs[a,b]

Variable	All Pts (*n* = 4,073,864)	I.V. Drug Exposure Category			
		Open Only (*n* = 3,707,453)	POC-Activated and Closed (*n* = 5,053)	POC-Activated (No Closed) (*n* = 99,149)	Closed (No POC) (*n* = 262,209)
Demographic					
Age, yr					
Mean ± S.D.	53.0 ± 23.2	52.5 ± 23.5	64.4 ± 15.5	59.1 ± 20.1	56.8 ± 20.2
Median (range)	56 (0–89)	56 (0–89)	67 (7–89)	63 (0–89)	59 (0–89)
Sex					
Male	1,639,625 (40.2)	1,483,990 (40.0)	2,519 (49.9)	44,563 (44.9)	108,553 (41.4)
Unknown	82 (0.0)	76 (0.0)	0	0	6 (0.0)
Race					
White	2,619,148 (64.3)	2,384,039 (64.3)	3,969 (78.5)	65,129 (65.7)	166,011 (63.3)
Black	582,310 (14.3)	534,015 (14.4)	319 (6.3)	18,755 (18.9)	29,221 (11.1)
Hispanic	306,942 (7.5)	283,893 (7.7)	435 (8.6)	6,070 (6.1)	16,544 (6.3)
Other or unknown	565,464 (13.9)	505,506 (13.6)	330 (6.5)	9,195 (9.3)	50,433 (19.2)
U.S. Census Bureau region					
Northeast	579,849 (14.2)	518,170 (14.0)	330 (6.5)	8,690 (8.8)	52,659 (20.1)
South	2,274,050 (55.8)	2,073,832 (55.9)	2,833 (56.1)	65,607 (66.2)	131,778 (50.3)
Midwest	583,067 (14.3)	509,663 (13.7)	1,793 (35.5)	16,047 (16.2)	55,564 (21.2)
West	636,898 (15.6)	605,788 (16.3)	97 (1.9)	8,805 (8.9)	22,208 (8.5)
Primary payer					
Medicare	1,664,566 (40.9)	1,498,796 (40.4)	2,972 (58.8)	51,680 (52.1)	111,118 (42.4)
Medicaid	605,140 (14.9)	569,504 (15.4)	220 (4.4)	11,047 (11.1)	24,369 (9.3)
Private	1,363,769 (33.5)	1,237,567 (33.4)	1,541 (30.5)	26,761 (27.0)	97,900 (37.3)
Other or unknown	440,389 (10.8)	401,586 (10.8)	320 (6.3)	9,661 (9.7)	28,822 (11.0)
Hospitalization					
Hospital size, by no. beds					
50–249	767,849 (18.8)	705,827 (19.0)	446 (8.8)	18,449 (18.6)	43,127 (16.4)
250–499	1,661,235 (40.8)	1,510,899 (40.8)	1,164 (23.0)	55,488 (56.0)	93,684 (35.7)
500–749	1,291,164 (31.7)	1,149,623 (31.0)	3,440 (68.1)	24,867 (25.1)	113,234 (43.2)
750–999	345,805 (8.5)	333,727 (9.0)	0	272 (0.3)	11,806 (4.5)
≥1,000	1,056 (0.0)	1,056 (0.0)	0	0	0
Unknown	6,755 (0.2)	6,321 (0.2)	3 (0.1)	73 (0.1)	358 (0.1)
Teaching hospital	2,351,221 (57.7)	2,162,552 (58.3)	3,405 (67.4)	50,123 (50.6)	135,141 (51.5)
Hospital location					
Urban	3,507,362 (86.1)	3,183,837 (85.9)	4,965 (98.3)	86,843 (87.6)	231,717 (88.4)
Rural	566,502 (13.9)	523,616 (14.1)	88 (1.7)	12,306 (12.4)	30,492 (11.6)
Yr of admission					
2007	1,411,074 (34.6)	1,281,319 (34.6)	2,387 (47.2)	36,480 (36.8)	90,888 (34.7)
2008	1,285,581 (31.6)	1,174,667 (31.7)	1,473 (29.2)	30,537 (30.8)	78,904 (30.1)
2009	1,377,209 (33.8)	1,251,467 (33.8)	1,193 (23.6)	32,132 (32.4)	92,417 (35.2)
Admission type					
Emergency	1,838,771 (45.1)	1,705,045 (46.0)	1,631 (32.3)	44,473 (44.9)	87,622 (33.4)
Urgent	710,092 (17.4)	657,242 (17.7)	605 (12.0)	11,710 (11.8)	40,535 (15.5)
Elective	1,409,403 (34.6)	1,234,672 (33.3)	2,740 (54.2)	41,573 (41.9)	130,418 (49.7)
Other or unknown	115,598 (2.8)	110,494 (3.0)	77 (1.5)	1,393 (1.4)	3,634 (1.4)
Transferred from another hospital	274,147 (6.7)	254,831 (6.9)	293 (5.8)	6,258 (6.3)	12,765 (4.9)
Hospital length of stay, days					
Mean ± S.D.	4.4 ± 5.5	4.4 ± 5.4	6.7 ± 7.2	5.8 ± 6.5	4.8 ± 5.6
Median (range)	3 (1–849)	3 (1–849)	4 (1–124)	4 (1–502)	3 (1–364)
At least 1 day on ICU	742,849 (18.2)	666,901 (18.0)	1,829 (36.2)	25,590 (25.8)	48,529 (18.5)

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Table 2 (*continued*)

Variable	All Pts (*n* = 4,073,864)	I.V. Drug Exposure Category: Open Only (*n* = 3,707,453)	POC-Activated and Closed (*n* = 5,053)	POC-Activated (No Closed) (*n* = 99,149)	Closed (No POC) (*n* = 262,209)
ICU length of stay, days					
Mean ± S.D.	0.7 ± 3.1	0.7 ± 3.1	1.9 ± 4.3	1.2 ± 3.4	0.8 ± 3.0
Median (range)	0 (0–364)	0 (0–310)	0 (0–58)	0 (0–140)	0 (0–364)
Additional risk factors[c]					
Surgery pt	2,438,843 (59.9)	2,139,760 (57.7)	4,532 (89.7)	71,113 (71.7)	223,438 (85.2)
Trauma pt	1,263,130 (31.0)	1,102,083 (29.7)	3,251 (64.3)	38,918 (39.3)	118,878 (45.3)
Central venous catheter use	121,514 (3.0)	105,519 (2.8)	388 (7.7)	5,751 (5.8)	9,856 (3.8)
Mechanical ventilator use	216,433 (5.3)	185,490 (5.0)	1,128 (22.3)	10,807 (10.9)	19,008 (7.2)
Hemodialysis	107,263 (2.6)	96,351 (2.6)	252 (5.0)	4,239 (4.3)	6,421 (2.4)
Malnutrition	122,910 (3.0)	109,788 (3.0)	258 (5.1)	4,643 (4.7)	8,221 (3.1)
Other infection	175,959 (4.3)	165,096 (4.5)	204 (4.0)	3,960 (4.0)	6,699 (2.6)

[a]BSI = bloodstream infection, POC = point of care, ICU = intensive care unit.
[b]All data are no. (%) unless specified otherwise.
[c]For patients with BSI, risk factors assessed using data recorded prior to BSI diagnosis.

POC-activated systems [17.2% versus 10.8%]). Multivariate adjusted analyses indicated that the exclusive use of either POC-activated systems or closed systems conferred less dramatic benefits.

It is curious that the combined use of both POC-activated and closed delivery systems was associated with a greater risk reduction than the use of closed systems exclusively. Given that closed systems, by design, require less manual handling (and thus have fewer potential contamination sites), we expected that their exclusive use would confer significant risk reductions relative to both POC-activated and open systems. However, our findings did not support that hypothesis. One possible explanation for this unexpected finding is that patients receiving i.v. administrations from both closed and POC-activated systems constituted a very small percentage of the study population (0.12%); this may have precluded full adjustment and skewed the results.

Another limitation of the study pertains to the data regarding antibiotic administrations, which can be both a source of and a treatment for hospital-acquired BSI. After excluding patients who received i.v. antibiotics before their BSI diagnosis, i.v. drug exposure via closed systems was associated with an 86% reduction in BSI risk, and i.v. drug exposure via POC-activated systems was associated with a 49% risk reduction. Among patients not receiving i.v. antibiotics, there were insufficient patients receiving both types of exposure to compute an effect estimate; this may

Table 3.
Risk of Bloodstream Infection in Patients Given Drugs I.V. by Point-of-Care (POC)-Activated or Closed Systems Relative to Administration by Open Systems Exclusively[a]

Exposure Group	Unadjusted RR (95% CI)	Adjusted OR (95% CI)[b]	Adjusted OR (No I.V. Antibiotics) (95% CI)[c]
POC-Activated and Closed	0.39 (0.21–0.72)	0.12 (0.06–0.23)	. . .[d]
POC-Activated (No Closed)	1.01 (0.93–1.10)	0.84 (0.76–0.93)	0.51 (0.39–0.65)
Closed (No POC)	0.63 (0.59–0.67)	0.88 (0.82–0.96)	0.14 (0.07–0.28)

[a]Estimates from logistic regression models include all covariates that modified the association between bloodstream infection and total i.v. exposure group by ≥10%. RR = risk ratio, CI = confidence interval, OR = odds ratio.
[b]Adjusted for nonantibiotic i.v. drug count, i.v. antibiotic count, other i.v. exposure count, days in hospital (prior to event), days in intensive care unit (ICU), trauma status, central venous catheter use, mechanical ventilation use, age, admission type, analgesic use, antifungal agent use, cardiac agent use, diuretic use, gastrointestinal agent use, hemostatic modifier use, hospital solution use, psychotherapeutic use, respiratory therapy agent use, and vascular agent use.
[c]Adjusted for nonantibiotic i.v. drug count, days in hospital (prior to event), days in ICU, central venous catheter use, mechanical ventilation use, age, hospital teaching status, urban or rural hospital location, admission type, analgesic use, antifungal agent use, cardiac agent use, hemostatic modifier use, hospital solution use, respiratory therapy agent use, and vascular agent use. No patients in this subgroup had exposures to both POC-activated and closed drug-delivery systems.
[d]Not applicable.

indicate misclassification pertaining to difficulties in identifying BSI cases using claims data. There is a financial incentive to record services accurately, but the documentation of a BSI diagnosis code could indicate a case of suspected BSI. It is also possible that billed antibiotics were administered prophylactically, particularly for surgical[19] and oncology patients.[20] Moreover, a documented blood culture could have been contaminated, thereby obscuring the source of BSI. For any of these reasons, a patient could have been included in our study as a BSI case in the absence of a confirmed diagnosis.

Another study limitation was that we did not control for all potential risk factors. In particular, information about infection-control practices that may have been in effect at institutions included in the analysis was unavailable in the claims database. In addition, other factors potentially associated with BSI risk (e.g., stem cell transplantation, neutropenia, chemotherapy use, number of i.v. lines, duration of line placement) were not controlled for. Although we do not readily conceive of these limitations having a major impact on the results, the effect of uncontrolled factors is uncertain.

Conclusion

Use of POC-activated and closed systems for i.v. drug delivery was associated with a significantly reduced risk of hospital-acquired BSI compared with exclusive use of open systems in a large population of hospitalized patients.

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Appendix A—Drugs with point-of-care-activated or closed i.v. delivery systems included in Premier Perspective Comparative Database

- Analgesics: fentanyl, morphine
- Antifungal agents: fluconazole
- Antiinfectives, systemic: ampicillin, azithromycin, aztreonam, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, clindamycin, gentamicin, metronidazole, nafcillin, piperacillin with tazobactam, ticarcillin with clavulanate, vancomycin
- Cardiac agents: dobutamine, dopamine, lidocaine, milrinone
- Diuretics: bumetanide, mannitol
- Gastrointestinal agents: famotidine, metoclopramide
- Hemostatic modifiers: heparin, tirofiban
- Hormones: oxytocin
- Hospital solutions: dextrose, hetastarch, sodium chloride
- Musculoskeletal agents: methocarbamol
- Neurologic disorder agents: phenytoin
- Parasympathetics: neostigmine
- Psychotherapeutics: lorazepam, midazolam
- Respiratory therapy agents: theophylline
- Vascular agents: cardene, diltiazem, labetalol, nicardipine

Appendix B—*International Statistical Classification of Diseases and Related Health Problems, 9th Revision* (*ICD-9*) and *Current Procedural Terminology, 4th Edition* (*CPT*) codes used in the study

- Infections
  - Bloodstream infection
    - *ICD-9* diagnosis: 038.x, 790.7, 995.91, 995.92
  - Other infections
    - *ICD-9* diagnosis: 002.0, 003.x, 004.1, 004.3, 004.8, 005.1, 005.89, 005.9, 008.00, 008.04, 008.09, 008.2, 008.3, 008.4x, 008.5, 008.61, 008.62, 008.63, 008.8, 009.0, 009.1, 009.2, 035, 036.0, 040.0, 041.x, 049.0, 054.3, 066.40,

066.49, 094.2, 130.0, 130.7, 130.9, 289.50, 289.53, 320.x, 323.4, 323.41, 323.6, 323.61, 323.7, 323.8x, 324.x, 372.00, 372.03, 382.00, 382.4, 382.9, 383.00, 383.02, 383.1, 383.9, 391.1, 397.9, 421.0, 421.9, 422.92, 461.x, 463, 464.00, 464.01, 465.8, 465.9, 466.0, 466.11, 466.19, 473.9, 475, 478.21, 478.22, 478.24, 480.x, 482.xx, 483.0, 483.1, 483.8, 510.0, 510.9, 513.0, 526.4, 528.3, 540.1, 566, 567.xx, 567.9, 569.5, 569.61, 572.0, 572.1, 574.xx, 575.0, 575.1x, 575.2, 575.5, 575.8, 575.9, 576.1, 590.xx, 597.0, 599.0, 601.0, 601.1, 601.2, 601.8, 601.9, 608.4, 611.0, 614.3, 614.4, 681.00, 681.02, 681.1x, 682.x, 686.1, 686.8, 686.9, 711.0x, 711.9x, 728.86, 730.0x, 730.1x, 730.2x, 785.4, 958.3, 996.6x, 998.51, 998.59

- Risk factors
  - Central venous catheter
    - *CPT:* 36488, 36489, 36490, 36491, 36555, 36556, 36557, 36558, 36560, 36561, 36563, 36565, 36566, 36568, 36569, 36570, 36571, 36575, 36576, 36578, 36580, 36581, 36582, 36583, 36584, 36585
  - Mechanical ventilator
    - *ICD-9* diagnosis: V46.1, V46.11, V46.12, V46.13, V46.14
    - *CPT:* 94656, 94657
  - Trauma
    - *ICD-9* diagnosis: 800–939.9
  - Hemodialysis
    - *ICD-9* procedure: 39.95
    - Billing charge clinical summary description including "hemodialysis services"
  - Malnutrition
    - *ICD-9* diagnosis: 260–269

Note: *ICD-9* codes reported as three digits will include all four- and five-digit codes beginning with the same three digits. For four-digit codes, any five-digit code beginning with the same four digits will also be included.