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Drug delivery systems' role in preventing central line–associated bacteraemia: an international perspective

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Abstract

Study objectives: An International Roundtable of infectious disease experts reviewed regional differences in approaches to healthcare-associated bacteraemia reduction, assessed the drug delivery system's role, and made best practice recommendations.

Results: Bloodstream infection (BSI) surveillance and clinical management practices vary greatly within and between nations, particularly between economically developed and low income countries. The solution is not to impose a single standard since actions that reduce BSIs and their optimal sequence also differ by a region's economic development level.

Conclusion: Education improves BSI rates most where rates are catastrophic; however, reducing already low rates requires more than education. Consequently, technology's greatest impact will be when drug delivery systems are already quite improved. The participants made seven recommendations.

Keywords

Bacteraemia, bloodstream infection, central line, drug delivery system, international surveillance

Introduction

Intravenous drug delivery systems should promote safety and reinforce practices that reduce healthcare-acquired bacteraemia risk. Economically developed nations have made progress in bloodstream infection (BSI) education and infrastructure, but they too face barriers. BSI reduction requires both new technologies and systems reengineering. Low and lower middle income countries must start at an earlier stage, with educational interventions, then development of an active surveillance infrastructure. An international roundtable of infectious disease experts examined regional differences aimed at wards reducing BSIs, assessed the drug delivery system's role, and made best practice recommendations.

Background

Despite substantial resources and emphasising hospital hygiene and safety, the US had 1.7 million healthcare-associated infections (HAIs) in 2002. HAIs resulted in 98,987 deaths, including 30,665 from BSIs [1]. Western Europe has BSI rates similar to those in the US. Germany tracks these data, in part, through the Krankenhaus

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Infektions Surveillance System (KISS). Since reporting is optional, not all hospitals report data. For hospitals participating for at least 36 months, there are striking differences between paediatric intensive care unit (ICU) (5.9 per 1,000 central vascular catheter (CVC)-days) and adult medical ICU (2.1 per 1,000 CVC-days) rates. Progress in lowering rates demonstrates how difficult and uneven improvements are: 2.1 per 1,000 CVC-days in 1997; 1.7 in 1998; 2.0 in 1999; then 1.7–1.8 until 2003, when it increased to 2.0 [2]. Other international trends are not encouraging. CVC-associated bloodstream infections per 1,000 CVC-days for eight developing country members of the International Nosocomial Control Consortium (INICC) ranged from 7.8 to 18.5 cases with a 35.2% crude mortality rate [3]. Twelve ICUs in India recently averaged 7.92 cases [4].

These data led the World Alliance for Patient Safety in 2005 to make HAI prevention its first Challenge, 'Clean Care is Safer Care' [5]. More than 110 ministries in developing and developed countries now support it [6].

Policies and surveillance

The lack of standardisation in data collection and relevant clinical practices threatens BSI control. Reduction begins with active surveillance though current data are not consistently comparable. Higher rates may be due to obtaining confirmatory blood cultures routinely, while lower rates may reflect missing data due to fewer blood cultures. A Swiss medical ICU's BSI rate of 19.8 cases per 1,000 CVC-days decreased to 5.8 when those without laboratory confirmation were excluded. Basing surveillance data solely on laboratory confirmed cases produces underestimates [7].

INICC, active in 30 countries spanning four continents, was created to improve the systematic collection of outcome and process surveillance data [8]. Rates that decline with active surveillance tend to reverse when it is discontinued. Consequently, surveillance data are charted against best practices, such as hand hygiene compliance, to detect recidivism.

INICC's case adjudication methodology is not restricted to positive cultures, which are often missing [9]. Instead, it includes active detection of clinical sepsis cases even when the culture is negative. INICC's process includes on-site consultation, data collection, and targeted feedback to encourage active case ascertainment. Actively observing patient-care practices is critical. When healthcare professionals describe what they do, they report an abstractly correct process. However, active surveillance provides a reality check – yielding information on what actually occurs.

International development

Brazil In 2003 Brazil wrote BSI prevention guidelines, including mandatory use of closed IV drug delivery systems.

China In Hong Kong public hospitals, the catheter-associated BSI rate in the ICU is a key performance indicator (KPI). Hospitals are required to report cases to the KPI centre at the headquarters and the data are summarised. The rate is then published and reported back to the hospitals as a part of the KPI's report, with all the other indicators, every three months. Mainland China does not have this type of reporting system. Since the 2008 Sichuan earthquake there have been discussions about starting an infection control department within the Department of Health.

Spain Current data reports do not distinguish between sepsis, a clinical entity whose reporting depends on the clinician's diagnostic acumen, and BSI, which requires pathogen documentation. The incidence of documented sepsis has been increasing in Spain as in many other developed countries. In a large teaching institution in Madrid, recording data for the last 25 years, the number of documented episodes of significant BSI increased from 16.0 episodes per 1,000 admissions in 1985 to 31.2 per 1,000 admissions in 2006 [10]. Over these 25 years the same methodology was used to identify and follow cases but the severity of the conditions of the admitted patients substantially increased.

United Kingdom In the UK there is an exemplary centralised, mandatory top-down national reporting of MRSA blood stream infections. These are published as league tables, assuring that the issue receives the chief executive's attention. A key constraint to further development is that catheter-related BSI are not yet identified separately. The delay in requiring more extensive mandatory reporting is due to the funding and surveillance infrastructure required. Investments that could demonstrate overall future benefit at a local level are often unfeasible without additional, perhaps external, funds to demonstrate the impact of ongoing active surveillance with feedback. A current example is that the introduction of mandatory screening for MRSA has been controversial despite evidence from individual units that feedback of surveillance data is associated with a downward trend in overall rates including bacteraemia.

South America Optional reporting is common but it creates a strong disincentive. A hospital reporting anything other than zero is worse than those hospitals that are not measuring infections. It is mandatory in Chile, but not in Argentina, Brazil, Columbia or Mexico.

Intravenous drug delivery system technologies

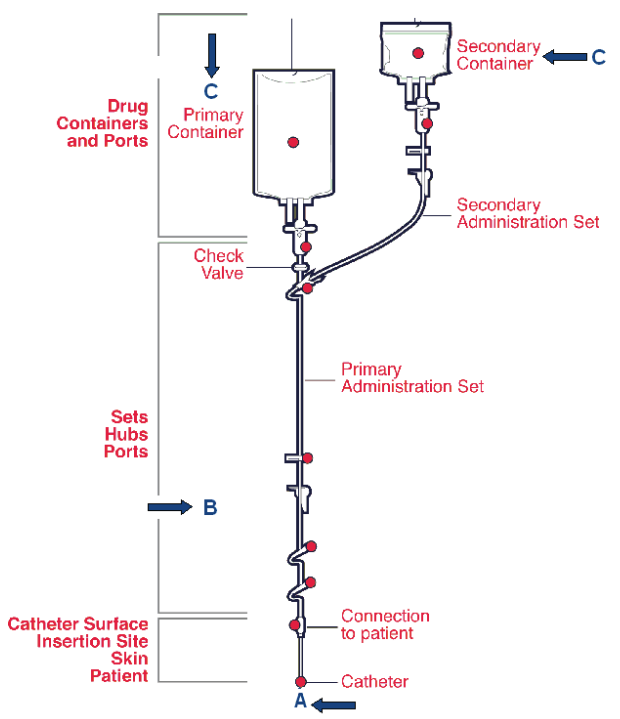
Bacteria have two ways to access the catheter tip: externally, from the peripheral environment of the catheter; and internally, from the hubs to the catheter tip (see Figure 1). The relative importance of each changes over time and with practice. External contamination is predominant, particularly at the time of insertion. With longer catheter use, intraluminal sources become the more prominent cause of healthcare-acquired bacteraemia. Contamination rates differ with technology. The sources of contamination risk and delivery system features are briefly reviewed.

The drug delivery system technology continuum

The main bacterial source in patients with healthcare-acquired bacteraemia is intraluminal. Any one bottle is in the delivery system for a short time, perhaps seven to eight hours, and is unlikely to be responsible for the majority of BSIs. There are three points of potential contamination:

- Catheter surface, insertion site, skin, patient
- Sets, hubs and ports
- Drug containers and ports. This raises the issue of which is the more important portal for intraluminal contamination, the hub or bacteria that went into the fluid. Delivery systems vary in their ability to prevent contamination from these sources.

Figure 1: Points of potential contamination



Source: Baxter Healthcare. Used with permission.

Open containers require venting to add the drug and multiple reconstitution steps, each posing a contamination risk. While there are no systematic empirical data, increasing the number of times a line is breached would be suspected to raise the likelihood of contamination. Unless there is a filter with an open container, its vent permits room air or other types of contamination. Data from China suggest that filters have a minimal salutary effect: filtered plastic or glass bottles had 10.6% positive cultures, compared to non-filtered bottles which were 12.4% positive [11]. For burettes, Macías reported an infusate-related contamination rate of 0.9% in a Mexican referral hospital, even though that hospital had an around-the-clock IV nurse team, active surveillance, an educational unit, and "a consolidated infusion control programme". They concluded that contamination reflected limited pharmacy IV admixture preparation and extensive nurse preparation on the ward [12].

Closed containers are fully collapsible and do not require external venting to empty the solution. The container residue after administration does not exceed 5% of the nominal volume [3]. The minibag is a widely used example: it comes with just a diluent in the bag, so the drug must be prepared and inserted manually. The most common US IV drug delivery practice is a nurse adding medication to a minibag, then using a secondary setup to infuse the admixture. US Pharmacopeia Chapter 797 limits nurses to mixing one dose and requires the pharmacy to do the remainder [13]. There is an exception for "immediate use", when the nurse can prepare and administer a drug immediately.

Closed admixture system reduces the risk of external contamination from exposure. With these systems, activation and administration without admixture are possible at the point-of-care. Examples include Minibag Plus and Add-Vantage.

Closed system. No formal definition of a closed system exists in the literature, but the concept covers a closed container that also contains the drug as a premixed ready-to-use liquid, or a frozen type of premix. A closed system virtually eliminates the opportunity for touch contamination to occur. As a result of drug manipulation, maintaining a closed system is recommended by Heeg [14]. Ideally, every drug that a facility administers should be available in this form; unfortunately, this is not currently possible for technical reasons. There is now a better understanding of the core concept that a 'closed system' requires four

elements: closed IV container, closed needleless connector, closed IV piggy bag container, and catheter insertion site integrity.

Despite similar hand hygiene compliance and sterile dressing care of the CVC site, CVC-associated BSI incidence in open systems was 6.52/1,000 CVC-days versus 2.36 in closed systems [15]. A recent study of four Italian ICUs, where two switched to closed containers, reported a drop from 8.2 to 3.5 CVC-associated BSIs per 1,000 CVC days [16].

Contamination and infection

Hand hygiene is the most basic change to prevent BSIs, but universal compliance is notoriously difficult to achieve as "… relying on fallible and microbially contaminated humans to perform flawlessly and with perfection is a doomed strategy that will inevitably lead to septic failures and contaminated doses." [17]

To improve practice, WHO initiated the *Five Moments for Hand Hygiene* campaign [18]. Baseline adherence was as low as 5%. Final adherence, after an intervention, ranged from 30% to 92% [19].

WHO emphasises that education is only one of many required elements. INICC compared baseline rates in similar Argentinean medical centres, followed by educational and performance feedback interventions. The intravascular device (IVD)-associated BSI per 1,000 IVD days started at 45.94. Following educational intervention it dropped to 17.06, and decreased even further, to 9.90, when coupled with performance feedback [20]. The study demonstrated the importance of performance feedback on basic clinical practices such as the presence of gauze on the IVD site, having a date on the IV administration set, and good gauze condition. With educational intervention alone the percentages for these were low and unchanged (53% to 56%, 0% to 0%, and 48.7% to 43%). After instituting performance feedback, these increased substantially (56% to 96.5%, 0% to 74%, and 43% to 89.6%).

A prospective study of six ICUs reported that syringes filled from 10-mL ampoules had contamination rates of 7% to 44% for nurse-prepared versus 1% for those prepared by pharmacy technicians. Rates for preparations using vials instead of ampoules were 2% for ICU nurses and 0% for pharmacy [21]. A comparison of pharmacist and technician in both traditional practice and a class 1000 cleanroom using USP Chapter 797 [13], medium-risk compounding procedures and "strict adherence to aseptic technique" detected no statistically significant difference in microbial contamination. The authors concluded the most important variable affecting microbial contamination was the aseptic technique of the personnel [22].

Biofilm formation is an additional risk. Within minutes of a catheter's insertion, biofilm formation begins. The bacterial inoculum required to initiate colonisation of the biofilm is small. Biofilms pose a barrier to antibiotic diffusion or penetration, so infected catheters must be replaced. Alternatives include the less successful 'lock technique' of injecting a high concentration antibimicrobial to penetrate the biofilm [23].

Quantifying quality: the US experience

The US healthcare system links outcomes measures, such as HAI, to payment policy. The Institute of Medicine's report, *To Err Is Human: Building a Safer Health Care System* [24], stimulated national demand for hospital quality performance measures. The Medicare programme established a list of Hospital Acquired Conditions, including vascular catheter-associated infections, that are considered a "serious preventable event" and will not pay for additional costs associated with their treatment unless documented on admission. This moves from reliance on process (what hospitals did to prevent infections) to outcomes (how successful hospitals are in preventing individual infections, not just their rate).

Summary

There are gaps between best and usual practice in BSI surveillance and drug delivery system management. Preventing CVC-associated bacteraemia begins with the fundamentals of hand hygiene, barrier control, and drug delivery system selection but also requires coordinated actions at multiple levels of the healthcare system. The infectious disease roundtable experts made seven recommendations for actions to prevent central line–associated BSIs. These are predicated on active surveillance.

1. **Phased strategy for BSI reduction:** Phase 1: Initially or when BSI rates are high, establish, monitor and enforce guidelines. Phase 2: emphasise educational interventions – at this point they can make a substantial impact. Once BSI rates have improved through education, training and active surveillance, then implement Phase 3: reengineering the drug delivery system. Device selection criteria can provide added improvements. Phase 3 gains will not be realised, however, if the first two phases are omitted or their sequence altered.
2. **Integrate risk management:** Link infection control with real-time quality management and multidisciplinary staff involvement, making infection control a fundamental component of clinical risk management.

3. **Principles for selecting the drug delivery system:** Viewed from the potential risk for external contamination, there are three main categories: i) vented, where the vial containing the drug must be manipulated; ii) vial and a bag, which only need to be connected; and, iii) premixed drug with diluent. Risk decreases from the first to the third category. Technologies provide options among these types, six recommended principles for selection are: i) optimal for patient safety for custom dosed drugs; ii) improved safety and productivity when ≥250 mL diluent is needed and an integrated closed system is not available; iii) optimal for patient safety when an integrated closed system is not available; iv) optimal for patient safety with more extensive pharmaceutical product selections; v) optimal for patient safety without refrigeration; and vi) optimal patient safety for stable molecules.
4. **Have a specialist-led, separate team for infection control:** A technology's realised impact is determined by the drug delivery system in which it is used, such as active or passive surveillance, human factors improvement initiatives, and/or continuous quality interventions. A separate infection control committee (ICC) is required, with a microbiologist as a regular member not as a consultant. The group's leader must have infection control as their primary professional focus. This specialist should direct active rather than passive surveillance. The ICC can perform surveillance, provide feedback and maintain a consistent focus on priorities for outcomes: what happens to the patient; process; what workers actually do; and supply; and what workers actually use.
5. **Evidence of safety:** There is sufficient evidence on the infusate's safety and on the superiority of closed over open containers.
6. **Closed container vs. closed system:** Roundtable experts agreed that evidence supporting closed containers over open containers is sufficient and further comparative research is not needed. Face validity suggests that a closed system should be preferable to a closed container. However, evidence demonstrating this potential advantage needs to be generated, preferably through clinical trials examining each product's use in an ICU. These trials should also monitor hub cultures, the number or rate of medication errors, ease of handling and preparation, and nurse satisfaction. Most endpoints of interest are low probability events, so the studies will require large numbers of subjects to have adequate statistical power to detect meaningful differences.
7. **Empirically determine risks from microscopic contamination:** Study whether microscopic contamination is sufficient to produce bloodstream infections.

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