Outbreak column 19: needleless connectors (NCs) tales from nine outbreaks

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Abstract

A critical review of historical outbreak reports that are still influencing practice today is presented. These outbreak reports were used as evidence in support of guideline recommendations and of the US Food and Drug Administration's (FDA) advisory notice requiring post-product surveillance for needleless connectors (NC) which have a positive displacement. Guideline recommendations were subsequently changed but not before other authorities had issued recommendations based on the original. All the above led some purchasers to look for different NC designs. The conclusions are that the evidence, as reported, does not support there being an increased risk from positive displacement NCs. Identified in this review were unsubstantiated claims, incompleteness in reporting of specifics, opinions considered as evidence and unexplored outbreak-provoking explanations.

Keywords

Blood stream infections, needleless connectors, outbreak

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Introduction

In the mid-2000s several outbreak reports were published suggesting a link between needleless connectors (NCs) and blood stream infections. This outbreak column is going to explore these reports to determine what was actually reported and question whether the inferences were sufficient to merit the actions taken, which were extreme. Overall it is another call to action for everyone—to interpret all science and scientists (including the author of this column) with due caution. Let's start with by examining the outbreaks and then looking at the chronology of consequences.

The Outbreak reports

Outbreak 1: Setting: Johns Hopkins Hospitals, Children's Centre

Reported increase: CRBSI 1.55 to 2.79 per 1000 catheter days $P = 0.01$

Maragakis et al. (2006) reported a significant increase in catheter-related bloodstream infection (CRBSI) temporally associated with the introduction of a NC 'SmartSite Plus

Needle-Free Valve'. The CRBSI data are presented as a graph of quarterly incidence density and although it clearly shows a sudden decrease in CRBSI following the NC change back, the rise on introduction is not as immediate—but still within the first quarter. This could be explained by a non-ubiquitous timed introduction. Maragakis et al. (2006) describe the introduced NC as being a 'Positive Pressure Mechanical Valve'. They acknowledge the necessary change in clamping-disconnection sequence and discuss how this was managed. They noted a non-significant increase in Gram-negative organisms (GNOs), which possibly suggests water ingress. The NC name as they write it is incomplete; the positive displacement version should have 'Positive Bolus' in the title. At the time there were two products both with very similar names 'Smartsite Plus Needle-free Valve' and 'Smartsite Plus Needle-free Valve Positive Bolus'; the former has a negative displacement

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(clamp before disconnection) and the later a positive displacement (clamp after disconnection). The picture presented in the article is of the 'Positive Bolus' NC. There are several possible explanations here: first, the established habit of clamping before disconnection was difficult to change and thus led to possible ingress. Second, although the authors considered they were dealing with a positive displacement NC, with such similar names a lookalike error (and thus systematic clamping sequence error) cannot be excluded from the evidence as presented. Finally, chance or something else changed at that time that led to the increase and associated decrease.

Outbreak 2: Setting: Haematology-Oncology unit in a 400-bed Geelong, Australia.

Reported increase CLABSI: 2.6 to 5.8 per 1000 catheter days $P = 0.031$

Field et al. (2007) report a significant CLABSI increase which followed a change to the CLC2000 (Abbott) NC. This device has a right-angled flow pathway. The change was to a positive displacement NC (clamp after disconnection). The Field et al. (2007) report makes no mention of the displacement, nor a clamping sequence change and how this was managed. They suggest that the reason for the increase might be 'difficulty in sterilizing (sic) the gap between the valve and the hub' (Field et al., 2007). The increased infection rate is reported to return to pre change levels once the split-septum NCs were reintroduced (Field et al., 2007). Other possible causes for the increase in CRBSI were looked for but none found. Unlike the Maragakis et al. (2006) study where the increase in central line-associated bloodstream infection (CLABSI) starts within the first quarter of the NC change, in the Field et al. (2007) report there is at least a 3-month delay from reported introduction of the new NC to any visible increase in the CLABSI rate. And the increase continued for a least 1 month after removal. This is explained by there being incomplete immediate change back. There would have been a stronger case if the report included confirmation that the infections arising after the official change-back were in patients' catheters where the CLC2000 was used. They further suggest that colonisation of the mechanical valve NC may be associated with increased rates of infection (Field et al., 2007). A significant change in microbiology to Gram-positive organisms (GPOs) was noted.

Outbreak 3: Setting: The Nebraska Medical Center (Omaha) is a 689-bed academic medical centre

Reported increase in CLABSI in critical care units (CCUs) and BSI in two cooperative transplant units

Rupp et al. (2007) report what they describe as a strong temporal increase in CLABSI per 1000 catheter days (or BSI per 1000 patient days) associated with the change from a split-septum NC (Interlink) to a 'luer-activated, positive

displacement intravascular access valve (SmartSite Plus)'. This report shows no change in microbiology. Three graphs are presented from three different units: CCU, in inpatient nursing units and in cooperative transplant units. The graphs show data from January 2003 to February 2006 (albeit there is misalignment in the placement of the months on the x-axis of 1 month). The CCU chart shows CLABSI per 1000 catheter days, the cooperative transplant unit chart shows BSI per 1000 patient days. The inpatient nursing units have too few data points to consider.

The NC was introduced in all units in the 'last week of February 2005'. In the CCUs, this introduction is followed immediately in March with a significant CLABSI increase. The removal of the novel NC commenced in June and was completed by the September. However, the September result is still well above baseline. Indeed, there is a significant difference in the CLABSI in the 6 months post (complete) removal of the NC with the baseline data (3.87 baseline; 5.59 post removal $P = 0.02$). If a NC is responsible for an immediate increase in CLABSI following introduction, then it would seem reasonable to assume that removal should similarly show a sudden decrease. Indicated in the data after a very stable CLABSI rate in 2003–2004 is a single highest data point (up to that point) 2 months prior to the NC introduction. All this suggests that something other than (or at least in addition to) the NC may have been affecting the CLABSI rate in this unit.

The graph for the cooperative transplant units (infections per 1000 patient days) shows the following:

- What appears to be a significant increase in 1 data point 4 months before the change to the novel NC (to approximately 17 BSI per 1000 patient days), for which there is no narrative.
- The increase in BSI reported as being concurrent with the introduction of the novel NC actually happens before, i.e. the February result is already high (when introduction was 'late February').
- The reintroduction of the old NC is accompanied by a significant immediate decrease. Unlike in the CCU chart which took 3 months to achieve.

Of note there was no increase in the contaminated blood culture rate which one would possibly have expected if cultures were being taken through contaminated NCs. Education had preceded introduction but there is no mention of a clamping sequence change. In short, the temporal associations reported following the introduction of the novel NC are not well-demonstrated in the graphics provided. Other explanations are possible.

Outbreak 4: Setting: 59 bed Long Term Acute Care, Charleston US

Reported increase in CLABSI from 1.79 to 5.95 per 1000 catheter days $P < 0.001$

Salgado et al. (2007) present a more convincing increase in CRBSI temporally associated with a NC change (and decrease following change back). The change was once again to the 'Smartsite plus needlefree valve'. They report that education was done repeatedly. A significant change to GNOs was also noted (Salgado et al., 2007), thus again suggesting possible water ingress. There is no mention as to whether this device was positive or negative with regard to displacement or whether the education included any necessary clamping sequence change. In addition, there is no mention of 'Positive Bolus'. There is no picture of the NC used. So, although a clear temporal association with the introduced NC the report contains no confirmatory information as to whether this was (or was thought to be a NC with positive displacement). The term 'needleless mechanical valve device' is used throughout. The lack of information on the clamping sequence limits the interpretations that can be made.

Outbreak 5: Settings: three hospitals in the US, two in Australia (ICUs, adult wards and oncology units)

Following a 2004 conference report of increased BSI associated with a switch from a split septum to a mechanic valve NCs in 2004, Jarvis et al. (2009) set out to determine if other centres had had similar experiences. Centres who had pre- and post-change data were invited to collaborate. All had used the CDC definitions and had similar approaches to central vascular catheter (CVC) care including adoption of prevention bundles. Other factors, such as changes in staffing levels that may have explained findings, were looked for and excluded. From all possible participating centres within and without the US, only five hospitals were included. The cumulative experiences of these five centres showed ubiquitous but not always significant increases in rates when changing from split-septum NCs to mechanical valve NCs. What would have made this study more impressive is the investigators looking for and including (if found) centres who changed NC and did not experience an increase. Focus groups highlighted that in all the centres there was poor NC change management, e.g. infection preventionists were excluded from the decision to change NC, some HCWs were unaware of the manufacturers' recommendations for proper NC use (specifically the clamping sequence). Compatibility with other components was poor and many stated there was sometime leakage and accumulation of fluid in the NCs. Hence to some extent this poor change management can be seen as doomed to fail regardless of the NC being introduced. Although no specifics of any internal designs were presented, Jarvis et al. (2009) considered the more complex design of the mechanical valve NC may have meant that pre-existing sub-optimal compliance with antiseptics was even more important than with non-mechanical valve NCs. The paper mentions education (and re-education) as being ineffective. Although

listing the SmartSite® as having positive displacement, Jarvis et al. (2009) exclude any further manufacturer's title details, i.e. the words 'Plus Needle Free Positive Bolus' are missing. Looking at the overall data as presented, it is clear that just two of the centres' are having a significant influence on the overall results, *P* values for the relative risk of increase being Hospital A (4 ICUs *P* = 0.16), Hospital B (6 ICUs *P* < 0.001), Hospital C (Adult wards *P* = 0.05; Adult ICU *P* = 0.67), Hospital D (ICU *P* = 0.60, Oncology ward *P* = 0.04) and Hospital E (Adult ICU *P* = 0.001) (Hospitals A–E *P* < 0.001).

Jarvis et al. (2009) state: 'In 3 participating facilities, where elevated hospital acquired (HA) HA-BSI rate could not be reduced despite multiple interventions, the use of split-septum NCs was readopted; at these facilities, HA-BSI rates significantly decreased to levels at or below pre-mechanical valve NC baseline levels. Because the infection practitioners, surveillance methods, practices, and patient populations had not changed, the reduced HA-BSI rates can be *attributable* to the change of NCs used.' Examination of their data reveals that in centre A, the novel NC was used for 39 months without a significant increase in CLABSI being detected (*P* = 0.16). Centre A also has a much higher starting CLABSI rate than other centres—from which a reduction could be expected with a focus on CVC care. Although there is a significant reduction in BSIs with the reintroduction in centre B's results, the rate does not reduce to the baseline levels. After reintroduction, centre C's results are significantly lower for the adult wards (unspecified number) but not for the four ICUs. The adult wards in centre C were using 1000 patient days and not catheter days as the denominator. Therefore, the results from Centres A, B and C do not seem to be sufficient to justify the statement regarding 'attributable to the change'.

What could have caused the change in rates?

When you have eliminated the impossible... Sherlock Holmes

Something must have happened. There were multiple reported increases not just in these papers but there is often mention of conference posters and presentations. Maragakis et al. (2007) report on a personal communication from Jarvis at the CDC who informs of 'thirteen additional institutions, including 1 large infusion company, reported similar findings in peer discussion groups at national meetings'. Yet for all this there are just five papers that subsequently get recited without due scrutiny. As these nine outbreaks contain inconsistencies in the reported microbial changes, and timing post introduction to increase in CLABSI, it is unlikely that these reports have a single narrative. Two do not demonstrate a clear temporal relationship (Field et al. and Rupp et al., and will be discussed no further). The Jarvis et al. (2009) combined studies provides no graphic data with which to

confirm the temporal association. Which leaves two reports that reveal possible similarities: Salgado et al. and Maragakis et al. both found an increase in GNOs, although not significant in one possibly explained by the duration of usage (8 versus 48 months). Both are with the SmartSite® NC and although reported as positive, both omit to use the manufacturer's title 'Positive Bolus'. The two outbreaks in the Jarvis paper involving SmartSite® could be of a similar pathology but there is insufficient information presented with regard to the microbiology changes.

The increase in infections with GNOs suggest water ingress. Water ingress could arise following an incorrect clamping sequence which leaves the fluid pathway open (discussed later). Incorrect clamping sequences could have arisen from:

- The 'education' focusing on explanation of what should be done rather than the psychomotor skills necessary to get the clamping sequence correct following each actuation, i.e. staff became aware of the need to change but were not yet competent/compliant in doing so.
- The education did not reach all people who needed to know.
- There were difficulties in quickly establishing a new habit for multiple staff.
- A lookalike error from the SmartSite® names, e.g. ordering the wrong NC and using a positive clamping sequence for a negative displacement NC. Thus leading to a mis-match between the education being provided and the device being used.

'Change introduces new forms of failure' (Cook)

There are other possible reasons for an increase in CLABSI in the published (and unpublished reports), for example:

- In some areas there was an overall lack of system monitoring of practices in general; infections in central lines were seen as inevitable and unpreventable; thus periodically leading to outbreaks.
- Pre-existing poor disinfection practice was exacerbated by NCs with a wider luer allowing more of what was on the outside of NCs to get on the inside.
- Change in intensity / methods of surveillance with the introduction of a new NC generating inconsistently collected data which is erroneously interpreted.
- As others 'had found' an increase associated with NC change people in individual centres went looking for a similar event – and found them (confirmation bias).
- The mechanical valve designs and design developments were so unfamiliar to the users and investigating epidemiologists that attributions were to made

them being the cause without due investigation of how this could be happening.

- Because of the awareness of the 'NC issues' other factors that could have explained the issues were left unexplored (availability bias – what you see being not all that there is).
- The novel NC were more cumbersome to change.
- Novel NCs were left unchanged for longer.
- Chance.

In five of the nine outbreak reports, the NCs are changed to one specific device – the SmartSite®; seven of the nine are reported to be to a positive displacement NC. However, if the SmartSite® device used was not the Positive Bolus version then only two of the seven changes are to positive displacement devices one of which did not achieve a statistical significant increase and in the other a temporal association has been excluded. Something happened to merit these reports – but the data as presented in the outbreak reports do not support the idea that the problem was either solely due to NCs or entirely due to NCs with a positive displacement.

What does the literature state about erroneous clamping sequence?

The answer is neither well-reported nor well-explained in the scientific or manufacturers' literature. Jarvis et al. (2009) states erroneously that 'For negative-pressure MV-NCs, one clamps the IV line and then disinfects the NC, whereas with positive-pressure MV-NCs, the reverse is true'. This obvious error of 'disinfects' for 'disconnects' was subsequently repeated (Btaiche et al., 2011) who wrote 'Despite the differences in manufacturers' disinfection recommendations whereby negative displacement valves are disinfected after the intravenous access is clamped and PPVs are disinfected before clamping, both negative and positive mechanical valves have been linked to increased CRBSI rate'. This is unsurprisingly referenced to Jarvis et al. (2009). The Joint Commission's (2012) guidance on preventing CLABSI states that: 'if the proper sequence is not followed, catheter occlusion can result, leading to an increased risk for CLABSI'. This statement is referenced to Btaiche et al. (2011) who did state, as quoted above, that both negative and positive mechanical valves have been linked to increased CRBSI; however, this statement was unrelated to erroneously applied clamping sequences. The only Btaiche et al. (2011) comment regarding what happens if the clamping sequence is not followed is: 'With negative displacement mechanical valves, the luer caps must be clamped before removing the syringe or tubing set to prevent blood from backing up into the catheter'. Leaving blood inside the catheter will increase occlusion risk and create the surface conditioning required for biofilm development. However, given that the reported temporal

associations are of CLABSI outbreaks and not occlusions, it is possible that some other pathogenesis was occurring. One further comment on disinfection and clamping sequence from Jarvis (2010) who states: 'If the clamping-disconnection sequence is not executed correctly, the risk of inadequate disinfection and contamination increases HA-BSI risk'. The second part of the sentence omits a clause that explains how an erroneous clamping sequence increases inadequate disinfection and the CLABSI risk. This missing clause may be explained by an alert from the Medical Device Agency (now MHRA) (MDA, 2008). The alert MDA/2008/016 was issued after several reports of 'the septum of these devices remaining in a recessed position following use'. The MDA specified that 'swabbing of the connector in this condition may lead to inadequate decontamination'. The MDA alert suggests that creation of the recess was thought to prevent adequate disinfection; this may be what Jarvis (2010) is referring to. However, one further line in the MDA alert explains that 'upon removal of the device, the top/septum should automatically return to its closed/home position and seal the fluid pathway'. If an erroneous clamping sequence leaves the septum, not just recessed but with the fluid pathway open, then a minimally opened fluid pathway would be sufficient to allow water and micro-organisms in. It could therefore be hypothesised that this explains the increase in CLABSI, and also the increase in CLABSI caused by GNOs.

The Consequences 1: recommendations from SHEA/IDSA

The Society of Healthcare Epidemiology of America and the Infectious Disease Society of America (SHEA/IDSA) produced a strategy to prevent CLABSI and used Outbreaks 1–4 to support their recommendation (Marschall et al., 2008):

Do not routinely use positive-pressure needleless connectors with mechanical valves before a thorough assessment of risks, benefits, and education regarding proper use (Marschall et al., 2008).

Edgar (2009) pointed out that no NC or other device should be introduced without a thorough assessment of risks, benefits and education regarding proper use. Edgar (2009) also criticised the recommendation as being 'overly broad in suggesting that 1) the use of all positive-pressure MVs lead to increased risk of CLABSI and 2) the use of only positive pressure MVs are associated with this risk'. The weighted BII evaluation was questioned given the scientific rigor of the studies which were observational, non-randomised, uncontrolled single-centre, with data collected retrospectively over different periods of time and devices not utilised according to manufacturers' instructions. Importantly, according to Edgar (2009) counter reports went ignored. In

the updating of the guidance, the Strategy regraded the 'optimal design' recommendation to an unresolved issue (Marschall et al., 2014).

The Consequences 2: the U.S. Government's Food and Drug Administration (FDA)

The FDA (2010) cited Outbreaks 1–5 in support of their requirement for manufacturers of 'positive displacement' NCs to undertake post-market surveillance. There is a general incompleteness in all of the reporting with regard to the manufacturers' product names, i.e. just using SmartSite® and none using 'Positive Bolus'. The FDA (2010) uses the term 'Administration Sets' at the end of 'SmartSite Needle Free Valve' – but still omits the words 'Positive Bolus'.

The Consequences 3: other guidance based on Marschall et al. (2008)

The Joint Commission produced guidelines to prevent CLABSI (Joint Commission, 2012). In repeating much of what has gone before and in a section on practices to be **avoided** it is stated: 'Use of positive-pressure NC with mechanical valves before conducting a thorough assessment of benefits, risks and staff education needs regarding their proper use'. They reference this to the now revised Marschall et al. (2008).

The Consequences 4: purchasers stopped using positive displacement NCs

Despite the changed recommendations from SHEA/IDSA, users of positive displacement NCs (who were not experiencing increases in CLABSI) were sufficiently concerned and looked to improve patient safety, e.g. Logan and Cvaa (2013). Their acute care hospital had used a positive displacement NC and had maintained a zero-CRBSI rate for 'a number of years'. They were prompted to change because of the adverse reports on positive displacement NCs (Logan and Cvaa, 2013). Harnage (2012) in marking the progress of and achievement in maintaining a zero-CLABSI advocate a neutral displacement NC and cite the publicised problems of 'positive displacement' catheters discussed earlier (which they did not experience).

A few other recent studies...

Tabak et al. (2014) claim that the novel study NC in their study, a positive displacement NC, 'has 8 of the 9 desired features outlined by infection control experts' (Tabak et al., 2014). The 'experts' (sic—pleural) referred to was a single author whose opinions were published in a

non-peer-reviewed journal (*Infection Control Today*) (Jarvis, 2010). Jarvis (2010) acknowledges the absence of evidence to support the design feature benefit claims. Indeed, the author states that: 'Many if not most of the aforementioned design features have not been specifically studied for their relative contribution to the risk of HA-BSIs associated with negative or positive pressure luer access mechanical valve NCs. Although their relationship to HA-BSIs is logical, it remains hypothetical.'

The Tabak et al. (2014) study (on which Jarvis is a co-author) was a meta-analysis of available studies comparing the MaxPlus®, with those NCs which were in current use; researchers found a lower CLABSI with the MaxPlus® (Tabak et al., 2014). Only one of the available studies found was in a peer-reviewed journal, the remaining six studies were found from conference abstracts. The Tabak et al. (2014) paper has limitations, i.e. a lack of studies in general, non-randomisation and a lack of peer-reviewed publications being included in the meta-analysis. It is interesting to note that just as the FDA (2010) were issuing their notice regarding positive displacement NCs, data collection on the encouraging effects of positive displacement NCs was being completed by Tabak et al. (2014). Thus, the 'improved engineering design' mentioned was actually being used as early as 2006, and five of the seven studies had completed data collection at least 12 months before the FDA released its alert. Therefore, the authors attribute a reduction in CLABSI to a novel design which at the time of publication was not that novel. Indeed, it works by a depressed plunger creating a fluid turbulent flow which reverts back to its original shape to seal the fluid pathway after disconnection. This NC does not have the desired fluid pathway characteristics advocated by Jarvis (2010). A recent *in vitro* study which looked at microbial ingress of eight NCs challenged with *S. aureus* found that the three positive displacement NCs had significantly less microbial ingress than the other five devices (Casey et al., 2015).

Some non-randomised uncontrolled studies make vast claims or hint at problems which can be persuasive to NC purchasing decision-makers. For example, researchers claimed that a change from positive or negative NCs to a zero displacement NC saved over \$3 million and 13 lives (Chernecky et al., 2014). The study involving six centres and a cumulative 140 study months provided a results section of one paragraph and one small table. (At the time of writing this paper the article by Chernecky et al. (2014) (of which Jarvis is also a co-author) was retracted. The retraction notice stated that 'the science was flawed'.)

Final comments

In most healthcare disasters, there are neither evil humans nor evil motives; just plenty of opportunities to get it wrong. Errors are generally brought about by a system inclusive of resource/workload mismatch, procedure complexity and cognitive

errors. There is no suggestion that people set out to deceive here, but obvious errors and omissions happened. The findings of opinions considered as evidence, unsubstantiated claims, incompleteness in reporting and unexplored outbreak-provoking explanations all led to—and continue to present—unwarranted alarm against some NCs. Sherlock Holmes in *The Sign of Four* (1890) said 'When you have eliminated the impossible that which remains, however improbable must be the truth'. The problem with some of these reports is that investigators failed to consider all that was possible.

The above events took months to uncover—time which individual practitioners do not have available. As people who interpret observations, we are prone to error and if we err in our interpretations we will consequently err in our decisions and actions. This column calls for the gold standard RCTs whenever possible and the scientific questioning of everyone, regardless of perceived experience and expertise.

As experts in infection control, we have become novices with regard to our knowledge of NC design and the implications thereof. These are the microbial gatekeepers of catheters and it is imperative we remain up to date with their designs and the evidence.

Conclusions

Five outbreak reports were used to support recommendations for action, in particular against NCs with positive displacement. However, because of what was reported, and what was omitted from the reports, it is possible to draw different conclusions. It is unlikely that a single narrative explains all events.

One explanation for the increase in CLABSI (in some of the reports) is an erroneous clamping sequence leaving the fluid pathway open (thus increasing infections with GNOs). There may have been other factors in the NCs' design, labelling, usage or CVC care in general that increased infection risks—but none can be confirmed from these reports. At present, there is an absence of evidence to support there being a superior, or inferior NC, by design feature or displacement (positive, negative or neutral) outbreak. The design features advocated by Jarvis (2010) require formal testing.

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