Infection control measures to decrease the burden of antimicrobial resistance in the critical care setting

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Purpose of review
The prevalence of multidrug-resistant organisms (MDROs) in ICUs is increasing worldwide. This review assesses the role of infection control measures, excluding antibiotic stewardship programs, in reducing the burden of resistance in ICUs.

Recent findings
The knowledge base about the effect of increased hand hygiene compliance in reducing the burden of methicillin-resistant \textit{Staphylococcus aureus} in ICUs has been improved. Universal decolonization with chlorhexidine body washing was associated with significant reduction in MDRO prevalence, but vigilance for emerging chlorhexidine resistance is required. A significant reduction of resistance for Gram-negative bacilli has been demonstrated with the use of selective decontamination, but further clinical trials are necessary before definitive conclusions can be drawn regarding long-term risk/benefit ratios.

Summary
In the recent years, several high-quality clinical studies have assessed the ability of various infection control measures in reducing the burden of antimicrobial resistance. Significant progress has been made in identifying interventions effective in preventing transmission of MDROs in ICUs, in particular, decolonization. However, it still remains impossible to determine the exact and relative importance of different infection control measures. Any approach must ultimately be tailored to the local epidemiology of the targeted ICU.

Keywords
ICU, infection control, multidrug-resistant organisms, prevention

INTRODUCTION
The emergence and spread of multidrug-resistant organisms (MDROs) in ICUs has been well documented \cite{1–3}. A recent meta-analysis which used pooled data of 63,740 ICU patients from more than 15 countries around the world showed that the overall admission prevalence of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) was 7% [95% confidence interval (CI) 5.8–8.3], with a higher prevalence in North America (8.9%, 95% CI 7.1–10.7) compared to North/Central Europe (4.4%, 95% CI 3.4–5.4) \cite{4}. In German ICUs, although the burden of MRSA did not increase over the past 11 years and was 4.2/1000 patient-days in 2011, the burden of third-generation cephalosporin-resistant \textit{Escherichia coli} and \textit{Klebsiella pneumoniae} more than quintupled (increased to 2.6 and 1.2/1000 patient-days, respectively). Worryingly, the burden of vancomycin-resistant \textit{Enterococcus faecium} (VRE) also increased dramatically from 0.1 to 0.8/1000 patient-days within 11 years. Resistance proportion of imipenem-resistant \textit{Pseudomonas aeruginosa}, \textit{Acinetobacter baumannii}, and \textit{K. pneumoniae} also showed a significant upward trend \cite{5}. In French ICUs, MRSA incidence decreased significantly from 2.46/1000 patient-days in 2003 to 0.92/1000 patient-days in 2010; in contrast, extended-spectrum \textit{b}-lactamase-producing Enterobacteriaceae (ESBL-Enterobacteriaceae) incidence increased significantly from 0.87/1000 to 1.56/1000 patient-days.

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DOI:10.1097/MCC.0000000000000126
The role of hand hygiene compliance in reducing the burden of MDROs was recently studied by Derde et al. [14**] in 13 European ICUs, with MRSA admission rate between 3.3 and 5.4%, as part of the MOSAR (Mastering hOspital Antimicrobial Resistance) study. The 26-month intervention study led to an improvement of hand hygiene compliance from 52 to 77% and demonstrated that chlorhexidine body washing, combined with hand hygiene enhancement, reduced MRSA acquisition by 3.6% per week. The gradual decrease in acquisition of MRSA coincided with a gradual increase in hand hygiene compliance, suggesting that hand hygiene improvement might have been an important component of the intervention since chlorhexidine body washing was successfully implemented immediately. This study, which demonstrated that it was feasible to increase hand hygiene compliance in high-workload settings, is the first cluster randomized trial to methodically confirm the beneficial role of increased hand hygiene compliance in reducing the burden of MRSA in ICUs. The same interventions did not reduce acquisition of highly resistant Enterobacteriaceae or VRE. This study supports enhancement of hand hygiene compliance as a method to reduce burden of MDRO in ICUs by reducing horizontal transmission, and demonstrates the long-term sustainability of hand hygiene promotion in busy ICUs.

ACTIVE SURVEILLANCE AND CONTACT PRECAUTIONS

The above-cited MOSAR study also demonstrated that the addition of screening and contact precaution strategy over and above adequate hand hygiene compliance and chlorhexidine body washing is of little value in reducing MRSA transmission [14**]. By contrast, an Australian before-and-after study implemented in a single ICU with low hand hygiene compliance (12–34%) and moderate MRSA rates (4.5 and 5% of carriage of MRSA at admission to the ICU in the control and the intervention phase, respectively), demonstrated that contact precautions, that is, use of gowns and gloves for MRSA-colonized/infected patients with single-room isolation or cohorting, were associated with a 60% reduction in MRSA acquisition [15**]. In the control phase, 2.7% of patients acquired MRSA compared with 1.3% in the intervention phase. After accounting for the a priori-determined covariates, the hazard ratio of MRSA acquisition in the intervention phase was significantly lower than in the control phase.

In a large US study involving 20 ICUs with higher rates of MRSA carriage at admission (between 7.8 and 10.5% in the control and the intervention phase, respectively), universal glove and gown use for all patient contacts compared with usual care
appeared beneficial in preventing MRSA acquisition (40.2% relative reduction in MRSA acquisition in the intervention ICUs compared with a 15.0% reduction in the control ICUs), which was the secondary outcome of the study [16**]. However, the primary outcome, which was MRSA and VRE acquisition, showed no significant reduction. Of note, hand hygiene compliance was only monitored on room entry (56.1% in the intervention group vs. 50.2% in the control group) and room exit (78.3% in the intervention group vs. 62.9% in the control group) and did not follow more stringent and widely validated hand hygiene observation criteria [17].

Overall, contact precautions have not shown their superiority over other strategies in decreasing the burden of endemic MDROs in the ICU setting. For MRSA, the importance of contact precautions in prevention of transmission [13] starts to weaken and hand hygiene compliance could be more effective. More than ever, the decision to adopt pathogen-specific screening and contact isolation should be made according to local context including relative burden of MDROs and available resources.

ENVIRONMENTAL CLEANING

The environment is a major reservoir of MDROs and could potentially play an intermediary role in their spread. Hence, cleaning of the hospital environment becomes an important infection control component. A cluster-randomized controlled trial examined the effect of enhanced cleaning vs. standard cleaning in US ICUs with single-occupant rooms. Intense enhanced daily cleaning of ICU rooms occupied by patients colonized with MRSA or multidrug-resistant A. baumannii (MDRAB) was associated with a nonsignificant reduction in contamination of healthcare workers’ (HCW) gowns and gloves after routine patient care. However, the authors did not assess hand hygiene compliance and its effect [18*]. A randomized clinical trial demonstrated that placing a copper alloy surface onto six common, highly touched objects in ICU rooms reduced MRSA or VRE colonization by 2.7-fold among patients admitted to copper rooms [19]. However, this study was promptly challenged on three important issues [20]: the study outcomes chosen and reported, the uncertainty concerning the methodology and determination of study end points, and inconsistency with the biological plausibility. These studies were unable to provide incontrovertible evidence to support the role of environmental cleaning in reducing the burden of antimicrobial resistance in the ICU setting.

DECOLONIZATION

Decolonization strategies include decolonization of the skin and the oropharyngeal or digestive tract.

Skin decolonization

Several high-quality studies have been published recently on universal decolonization of patients, independent of their MDRO carriage status. Climo et al. [21**] compared daily bathing with chlorhexidine-impregnated washcloths to nonantimicrobial washcloths in a cluster-crossover study of nine ICUs with high MDRO prevalence (between 15.1 and 16.3% for VRE and between 12.8 and 13.8% for MRSA). The intervention significantly reduced the acquisition of VRE by 25% (4.28 vs. 3.21/1000 patient-days), but not MRSA. The emergence of MRSA or VRE isolates with high-level resistance to chlorhexidine was not detected. It should be noted that this analysis did not account for clustering effects and competing outcomes, and therefore might have overestimated the statistical significance of the findings [22]. In another US study, 74 ICUs were randomly assigned to one of three groups: MRSA screening and isolation; targeted decolonization; and universal decolonization with mupirocin nasal ointment combined with chlorhexidine body washing [23**]. Universal decolonization was associated with significant reductions of clinical cultures yielding MRSA, and all-cause bloodstream infections, but not MRSA bloodstream infections. The effect on infections due to pathogens that are not eliminated by mupirocin application suggests that chlorhexidine baths were the key components of the intervention. Further support for chlorhexidine body washing as an acceptable infection control measure came from a surgical ICU study, which used time-series analysis to evaluate the impact of daily chlorhexidine bathing of patients admitted to the ICU. After adjusting for differences in comorbidities, severity of illness and seasonality, the intervention resulted in decrease in transmission and infection with S. aureus, including MRSA [24*].

Universal decolonization with chlorhexidine body washing, with or without nasal mupirocin, can decrease acquisition of MRSA or VRE, with some reduction in infections. However, its effect on Gram-negative organisms remains controversial. As demonstrated by Derde et al. [14**] enhancement of hand hygiene compliance plays an important role in reducing ICU MDRO burden as well. Considering the high probability of emergence of resistance to chlorhexidine and mupirocin, cautious monitoring is warranted should an institution opt to implement universal chlorhexidine decolonization in ICUs,
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Setting</th>
<th>Period</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derde et al. [14**]</td>
<td>Combination of interrupted time series and cluster-randomized design</td>
<td>13 European ICUs</td>
<td>May 2008–April 2011</td>
<td>Phase 2: combination of HH enhancement and chlorhexidine body wash; phase 3: randomization into conventional or rapid screening for MRSA, VRE and highly resistant Enterobacteriaceae with contact precautions for identified carriers</td>
<td>HH enhancement with chlorhexidine body washing reduced MRSA acquisition</td>
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<tr>
<td></td>
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<td></td>
<td>Screening and contact precautions have no added value in the setting of high HH compliance and chlorhexidine body washing</td>
</tr>
<tr>
<td>Salama et al. [31]</td>
<td>Interventional before and after study</td>
<td>ICU and cardiac intensive unit in a tertiary care center</td>
<td>Feb 2011–Aug 2011</td>
<td>A combination of lectures, visual reminders, HH instruction materials, strategic placement of alcohol-based hand rub and feedback</td>
<td>Significant increase in HH compliance was associated with significant reduction in HAI and incidence of MDROs</td>
</tr>
<tr>
<td>Benenson et al. [32]</td>
<td>Prospective surveillance</td>
<td>2 NICUs in one center</td>
<td>Jan 2006–Dec 2009</td>
<td>Weekly surveillance culture for ESBL–K. pneumoniae, contact precautions and cohort nursing for positive cases</td>
<td>Significant reduction in ESBL–K. pneumoniae acquisition</td>
</tr>
<tr>
<td>Marshall et al. [15**]</td>
<td>Prospective interrupted time series design</td>
<td>ICU in one center</td>
<td>May 2007–Sept 2009</td>
<td>Rapid PCR MRSA screening and contact precautions with single room isolation or cohorting</td>
<td>Significant reduction in MRSA acquisition, both for trend and level</td>
</tr>
<tr>
<td>Harris et al. [16**]</td>
<td>Cluster-randomized trial</td>
<td>20 medical and surgical ICUs in 20 hospitals</td>
<td>Jan 2012–Oct 2012</td>
<td>Universal glove and gown usage in ICUs compared with standard care</td>
<td>No significant reduction in MRSA or VRE acquisition (primary outcome) between intervention and control groups, a significant reduction in MRSA acquisition (secondary outcome)</td>
</tr>
<tr>
<td>Marioka et al. [33]</td>
<td>Before and after intervention study</td>
<td>NICU in one center</td>
<td>Jan 2007–Dec 2010</td>
<td>Preemptive contact precautions for outborn infants</td>
<td>Incidence of healthcare-associated MRSA transmission reduced significantly</td>
</tr>
<tr>
<td>Salgado et al. [19]</td>
<td>Randomized controlled trial</td>
<td>3 ICUs in 3 hospitals</td>
<td>July 2010–June 2011</td>
<td>Rooms with copper alloy surface</td>
<td>Rate of HAI and/or MRSA or VRE colonization significantly lower in ICU rooms with copper alloy surfaces</td>
</tr>
<tr>
<td>Climo et al. [21**]</td>
<td>Cluster-randomized, 2 period cross-over trial</td>
<td>6 adult ICUs and BMTUs</td>
<td>Aug 2007–Feb 2009</td>
<td>Screening and contact precautions with chlorhexidine body wash</td>
<td>Significant reduction in overall hospital acquired BSI. MRSA and VRE acquisition reduced significantly</td>
</tr>
<tr>
<td>Huang et al. [23**]</td>
<td>Cluster-randomized, pragmatic, comparative effectiveness trial</td>
<td>74 adult ICUs and BMTUs in 43 hospitals</td>
<td>Jan 2009–Sept 2011</td>
<td>Comparison between screening and contact precautions, targeted decolonization and universal decolonization</td>
<td>MRSA clinical cultures and BSI reduced with all interventions but universal decolonization was most effective</td>
</tr>
</tbody>
</table>
Selective decontamination

Selective oropharyngeal decontamination (SOD) and selective digestive decontamination (SDD) are generally defined as the prophylactic applications of topical, nonabsorbable antimicrobials in the oropharynx for the first strategy, and in the oropharynx and stomach accompanied by systemic antimicrobials for the second one. Several studies have shown a reduction of ventilator-associated pneumonia (VAP), but a reduction in mortality has been demonstrated less consistently. These strategies are not recommended in international guidelines for VAP prevention due to fear that they may spur an increase in antimicrobial-resistant pathogens.

A recent meta-analysis evaluated 64 unique studies, mostly from the Netherlands (18 studies, 28%), for the effect of selective decontamination on rates of colonization or infection with MDROs in ICU patients. Surprisingly, the authors detected a statistically significant reduction of resistance for polymyxin-resistant and third-generation cephalosporin-resistant Gram-negative bacilli (GNB) in recipients of selective decontamination compared with those who received no intervention. There was no difference between the two groups in Gram-positive antimicrobial-resistant pathogens including MRSA and VRE, and aminoglycoside-resistant or fluoroquinolone-resistant GNB. The significance of this finding is limited by difficulties in understanding the precise mechanism of the decrease. Moreover, long-term follow-up over many years will be necessary to assess the real effect of selective decontamination on antimicrobial resistance.

A Dutch team recently confirmed these results with a large 4-year ecological study involving 38 ICUs. The introduction of SOD or SDD was associated with a reduction in resistance rates of GNB for all the antimicrobial agents studied, that is, colistin, tobramycin, ciprofloxacin, ceftazidime and cefotaxime/ceftriaxone, in blood and respiratory tract specimens. In ICUs that did not use SOD or SDD, the rates of colistin-resistant GNB increased over time. As caveats, it should be noted that this study had been performed in a country with a low prevalence of antimicrobial resistance and the follow-up of patients had been restricted to the period of their ICU stay. Data from two Dutch cohort studies demonstrated that prolonged use of colistin as part of SDD and SOD was not associated with increased acquisition of colistin-resistant GNB in the respiratory tract. The overall conversion rate from colistin susceptibility to resistance in the intestinal tract and it should ideally be coupled with enhancement in hand hygiene compliance.
was below 1 conversion/1000 patient-days at risk; however, it was five-fold higher during persistent GNB colonization and 15-fold higher during carriage with tobramycin-resistant GNB. On the contrary, introduction of SDD during an outbreak of ESBL–K. pneumoniae in a Dutch ICU and its continued implementation over 5 years was followed by a clear increase in the detection of pathogens intrinsically resistant to colistin [28*]. Moreover, both the occurrence and the proportion of tobramycin resistance among pathogens intrinsically resistant to colistin, as well as occurrence of bacteremia caused by organisms resistant to SDD, increased under the use of SDD [28*].

A Dutch team has recently evaluated the impact of SDD on gut microbiota and resistome in a single ICU patient during and after an ICU stay through several metagenomic approaches, and also determined the relative abundance of two aminoglycoside resistance genes in longitudinally collected samples from 12 ICU patients who received SDD [29*]. This interesting study has two main conclusions. One was that ICU hospitalization and simultaneous application of SDD has large, highly individualized effects on the gut resistome of ICU patients with routinely performed microbiological cultures unable to identify resistance. Another one was that selection for transferable antibiotic resistance genes in anaerobic commensal bacteria with SDD could impact the risk of transfer of antibiotic resistance genes to opportunistic pathogens.

Despite recent demonstration that selective decontamination is cost-effective [30*], well designed cluster-randomized clinical trials in both low and high-endemicity settings, with adequate tools for measuring resistance, regular sampling of patients (after ICU discharge), adjustments for other infection control measures and patient characteristics, and long-term follow-up of patients seem necessary before we can make definitive conclusion of its positive and negative impacts. Currently, a European Union-funded study (R-Gnosis SDD trial) is under way to elucidate this crucial question.

Selected, recently published infection control studies investigating different measures to decrease the burden of endemic MDROs are summarized in Table 1.

### PARTICULAR OUTBREAK INVESTIGATIONS

MDRO outbreaks have been widely described in adult and neonatal ICUs. Most of the outbreaks were controlled with multimodal intervention programs.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Setting</th>
<th>Organism</th>
<th>No. of patients</th>
<th>Duration</th>
<th>Multimodal interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourigault et al.</td>
<td>ICU</td>
<td>MDRAB</td>
<td>29</td>
<td>9 months</td>
<td>Chlorhexidine bathing, restriction of admissions of new patients, cohorting of HCWs</td>
</tr>
<tr>
<td>Landelle et al.</td>
<td>ICU</td>
<td>MDRAB</td>
<td>86</td>
<td>18 months</td>
<td>Chlorhexidine bathing, restriction of admissions of new patients, cohorting HCWs and patients, and unit closure</td>
</tr>
<tr>
<td>Cantey et al.</td>
<td>NICU</td>
<td>ESBL–K. pneumoniae</td>
<td>11</td>
<td>3 weeks</td>
<td>Alleviation of overcrowding, cohorting of HCWs and patients</td>
</tr>
<tr>
<td>Giuffre et al.</td>
<td>NICU</td>
<td>ESBL–E. coli</td>
<td>15</td>
<td>5 months</td>
<td>Restriction of admissions of new patients, cohorting of HCWs</td>
</tr>
<tr>
<td>Fabbri et al.</td>
<td>NICU</td>
<td>Ampicillin/piperacillin-resistant K. pneumoniae</td>
<td>6</td>
<td>2 months</td>
<td>Restriction of admissions of new patients</td>
</tr>
<tr>
<td>Poulou et al.</td>
<td>ICU</td>
<td>Carbapenem-resistant K. pneumoniae</td>
<td>19</td>
<td>7 months</td>
<td>Cohort of HCWs</td>
</tr>
<tr>
<td>Pusch et al.</td>
<td>NICU</td>
<td>VRE</td>
<td>14</td>
<td>17 months</td>
<td>Cohort of HCWs and patients</td>
</tr>
<tr>
<td>Giuffre et al.</td>
<td>NICU</td>
<td>Carbapenem-resistant K. pneumoniae</td>
<td>10</td>
<td>2 months</td>
<td>Cohort of patients</td>
</tr>
<tr>
<td>Iosifidis et al.</td>
<td>NICU</td>
<td>VRE</td>
<td>101</td>
<td>25 weeks</td>
<td>Cohort of patients</td>
</tr>
<tr>
<td>Iacobelli et al.</td>
<td>ICU</td>
<td>MRSA</td>
<td>NA – before and after study</td>
<td>3 years</td>
<td>Multidisciplinary quality improvement approach</td>
</tr>
</tbody>
</table>

ESBL, extended-spectrum β-lactamase; HCW, healthcare worker; MDRAB, multidrug-resistant A. baumannii; MRSA, methicillin-resistant Staphylococcus aureus; NA, not applicable; NICU, neonatal intensive care unit; VRE, vancomycin-resistant Enterococci.
Consisting of implementation or reinforcement of adherence to standard precautions (with survey of hand hygiene compliance and feedback), screening of patients, contact precautions for all carriers of MDROs, audit of HCW practices and education, strict environmental cleaning policy for rooms and for any item that might have come into contact with carriers, being implemented in various combinations. However, some outbreaks can be recalcitrant needing additional infection control measures such as chlorhexidine bathing [36,37], alleviation of overcrowding [38], restriction of admissions of new patients [36,37,39,40], cohorting of HCWs [36–39,41,42], cohorting of patients [37,38,42–44], and unit closure [37]. Iacobelli et al. [45] reported a successful reduction in invasive MRSA infections through a sustainable prevention strategy designed by HCWs themselves using a multidisciplinary quality improvement approach. Selected, recently published outbreak control studies are summarized in Table 2.

Noteworthy, a recent study has demonstrated the added value of sophisticated outbreak detection software to analyze a wide range of species groups and resistance profile combinations. It showed frequent resistance outbreaks with a distribution pattern consistent with interspecies transmission of resistance elements. A better understanding of the relative contribution of the several mechanisms of resistance emergence and spread on ICU is needed to inform antimicrobial stewardship and infection control programs [46].

**CONCLUSION**

The prevalence of MDROs in ICUs is increasing worldwide. In recent years, several high-quality controlled clinical studies have assessed the role of various infection-control measures in reducing the burden of antimicrobial resistance. Progress is being made in identifying effective interventions to prevent transmission of MDROs in ICUs, in particular, decolonization. Any approach must ultimately be tailored to the local epidemiology of the targeted ICU and should also consider the type of resources available.

**Acknowledgements**

None.

**Conflicts of interest**

S.H. reports having received peer-reviewed research grants funded by Pfizer and B. Braun; he is also a member of the speakers’ bureau for bioMérieux and a member of the advisory board of Destiny Pharma, bioMérieux, and DaVolterra. All other authors report no conflicts of interest relevant to this article.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Infectious diseases


A cluster-randomized controlled trial assessing whether enhanced daily cleaning would reduce contamination of healthcare worker gowns and gloves with MRSA or MDRAB.


A multicenter, cluster-randomized, nonblinded crossover trial to evaluate the effect of daily bathing with chlorhexidine-imregnated washcloths on the acquisition of MDROs and the incidence of hospital-acquired bloodstream infections. Daily bathing with chlorhexidine-imregnated washcloths significantly reduced the risks of acquisition of MDROs and development of hospital-acquired bloodstream infections.


A pragmatic, cluster-randomized trial randomly assigned to one of three strategies, adult ICUs patients: MRSA screening and isolation; targeted decolonization (i.e. screening, isolation, and decolonization of MRSA carriers); universal decolonization (i.e. no screening and decolonization of all patients). Universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen.


A prospective preintervention study with control unit to determine whether daily bathing with chlorhexidine-based soap decreased MRSA transmission and ICU-acquired S. aureus infection among ICU patients.


A meta-analysis of the effect of SDD and SOD on the rates of colonization or infection with antimicrobial-resistant pathogens in ICU patients. No relation was found between the use of SDD and SOD and the development of antimicrobial resistance in pathogens in ICU patients.


An ecologic study to determine trends in antibiotic resistance among gram-negative bacteria in 38 Dutch ICUs using and not using SOD/SDD.


A study assessing quantified effects of selective decontamination on acquisition of colistin-resistant GNB.


A retrospective investigation of the impact of SDD, applied for 8 years as part of an infection control program for the control of an outbreak with ESBL-producing K. pneumoniae in an ICU, on resistance among aerobic GNB.

27. Buelow E, Gonzalez TB, Versluis D, et al. Evaluation of the impact of SDD on the gut microbiota and resistome in a single ICU patient during and after an ICU stay by several metagenomic approaches; determination of the relative abundance of two aminoglycoside resistance genes from 12 ICU patients who received SDD.

A post-hoc analysis of a previously performed cluster-randomized trial to determine costs and effects of SDD and SOD as compared with standard care (i.e. no SDD/SOD) from a healthcare perspective in the Dutch ICUs.


An unmasked, cluster-randomized, two-period crossover trial assessing whether daily bathing in chlorhexidine compared with standard bathing practices would reduce bacteremia in critically ill children.


Use of a software package to determine the burden of species and resistance outbreaks in two adjacent ICUs and to look for evidence of clustering of resistance outbreaks consistent with interspecies transmission of resistance elements.