Vancomycin-resistant enterococci: The value of infection control and antibiotic control policy

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Vancomycin-resistant enterococci (VRE) represent a major challenge for the Canadian health care system. The clinical significance of VRE in the Canadian health care system has increased over the past two decades, with outbreaks reported in Ontario and Quebec, although most provinces have been affected. This organism has been a substantial human and financial burden for Canadian institutions. VRE have been shown to be associated with an increased mortality, a longer hospital stay and a much higher overall cost compared with vancomycin-susceptible strains.

Enterococci are now the third most important nosocomial pathogen in American intensive care units. The two most common species, *Enterococcus faecalis* and *Enterococcus faecium*, have shown remarkable adaptability in responding to antibiotics. The arrival of VRE in Canada has forced hospitals to implement stringent and costly infection control measures. A multifaceted approach, including antibiotic restriction and stringent infection control measures, is important in managing VRE prevalence in Canadian institutions.

Key Words: Infection control; Vancomycin-resistant enterococci

After Fleming's discovery in the 1930s and the subsequent efforts by Florey and Chain in the 1940s to make sufficient quantities of penicillin, it did not take long for bacteria, especially some Gram-positive species such as staphylococci, to develop resistance.

Enterococci, which are part of the normal flora of the digestive tract, are playing an increasingly important clinical role. The importance of this species has steadily grown over the past two decades. It is now the third most important nosocomial pathogen in American intensive care units (ICUs) (1). The two most common species, *Enterococcus faecalis* and *Enterococcus faecium*, have shown remarkable adaptability to antibiotics. They have become successively resistant to tetracyclines, erythromycins, aminoglycosides, ampicillin and, lastly, vancomycin (2).

Vancomycin-resistant enterococci (VRE) represent a major challenge for the Canadian health care system. Its presence within Canadian hospitals adds an additional human and financial burden on our institutions. The introduction of this strain in our environment has required hospitals to implement stringent and costly infection control measures (3). It has also heightened concerns about the potential indiscriminate use of antibiotics.

Les entérocoques résistants à la vancomycine : L'utilité des mesures de lutte contre les infections et des restrictions d'emploi des antibiotiques

Les entérocoques résistants à la vancomycine (ERV) constituent un problème de taille pour le système de soins de santé au Canada. L'importance clinique des ERV dans le système a augmenté au cours des deux dernières décennies; en effet, des écloisions ont été signalées en Ontario et au Québec, mais la plupart des provinces n'ont pas été épargnées. Les infections à ces micro-organismes imposent un lourd fardeau financier et humain aux établissements touchés. Les infections aux ERV sont associées à une mortalité accrue, à une prolongation des séjours à l'hôpital et à une augmentation très importante des frais généraux par rapport aux infections causées par des souches sensibles à la vancomycine. Les entérocoques forment maintenant la troisième famille d'agents pathogènes à l'origine des infections nosocomiales dans les services de soins intensifs en Amérique. Les deux espèces les plus courantes, *Enterococcus faecalis* et *Enterococcus faecium*, montrent une adaptabilité remarquable aux antibiotiques. La transmission de ces micro-organismes au Canada a obligé les hôpitaux à recourir à des mesures de lutte contre les infections, à la fois rigoureuses et coûteuses. La mise en œuvre d'une approche complexe, comportant entre autres une restriction d'emploi des antibiotiques et des mesures rigoureuses de lutte contre les infections, constitue un élément important de la gestion de la prévalence des infections aux ERV dans les établissements au Canada.

The origin of vancomycin resistance remains unclear. Avoparcin, a glycopeptide mainly used in Europe as a growth promoter in animal feeds, may be responsible for selecting VRE in farm animals. The latter may have been transmitted to humans through the food chain, or by direct contact to people close to the cattle industry (2).

EPIDEMIOLOGY

Since its initial identification in the late 1980s, VRE have been reported around the world, with variable prevalence among countries. Some European countries, such as France, have a high prevalence of VRE. In the United States, the National Nosocomial Infection Surveillance Program reported a continually increasing proportion of resistant enterococci throughout the 1990s, especially in the ICU setting (1). The percentage of VRE in American ICUs increased from 0.4% in 1989 to 23.2% in 1997. In parallel, in the non-ICU setting, the rate went from 0.3% to 15.4% (1). VRE outbreaks in Canada have been reported mainly in Ontario and Quebec, although most other provinces have also been affected (British Columbia and Nova Scotia) (4). These outbreaks were contained after introducing stringent infection control measures. One study involving 38 medical centres described the prevalence

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TABLE 1
Recommendations for limiting vancomycin-resistant enterococci transmission

Precautions

- Private room or cohorting
- Gloves
- Removal of gloves and gown before leaving the room
- Washing of hands with an antiseptic soap or a waterless antiseptic agent
- Gowns (most of the time)
- Rectal cultures (roommates and screening)
- Dedicated equipment
- Precautions in place until patient's cultures are negative on at least three occasions, one week apart
- Colonized and infected patients identified when transferred to another facility or within the hospital
- Tagging of colonized or infected patients on a computer system (for readmission or outpatient visits)

Patients cohorting

- Assigning of patients to geographical cohorts

Staff cohorting

- Assigning of nurses to patient cohorts

Data from reference 3

of VRE in enterococci isolated from the urinary tract. Only three strains were found in Canada, compared with 697 in the United States (5). An international study showed a much higher proportion of VRE in the United States than in Canada and Latin America. For example, the VRE rate was 16.3% versus 1.3% in bloodstream isolates in the United States and Canada, respectively (6).

VRE in Canada were mainly an issue of outbreaks in selected high-risk units, including nephrology wards, hemodialysis and ICUs. The aggressive approach taken by Canadian institutions when these outbreaks were recognized may have limited the spread of this microorganism.

RISK FACTORS

Unlike other antibiotic-resistant microorganisms, such as *Streptococcus pneumoniae* or the newly problematic community-acquired methicillin-resistant *Staphylococcus aureus*, VRE have been restricted to high-risk patients. Virtually all VRE-colonized or -infected patients had at least one significant medical problem (2). The principally identified risk factors were severe underlying conditions, such as immunosuppression, intra-abdominal surgery, hemodialysis and previous antimicrobial therapy with vancomycin or cephalosporins (2,4). Once colonized, only a small fraction of patients develop a significant infection. In a prospective study (7) of patients with liver and kidney transplants, only six of 52 patients (11.3%) initially colonized developed an infection.

CLINICAL IMPLICATIONS OF VRE

VRE have been shown to be associated with an increased mortality risk, longer hospital stay and much higher overall cost compared with vancomycin-susceptible strains (8). In one study, Lucas et al (9) reported the attributable crude fatality rate to be 27% for vancomycin-susceptible enterococci and 45% for VRE. However, patients with VRE infections are in poorer medical condition, and this may contribute to some mortality differences.

TRANSMISSION AND INFECTION CONTROL

VRE have been shown to spread rapidly in outbreak situations. Contact precautions, patient cohorting and staff cohorting have been recommended to limit the transmission of VRE (3) (Table 1). During outbreaks of VRE, there is extensive colonization of patient and staff digestive tracts. This asymptomatic carriage can last months or years (10). After experimental inoculation, VRE can survive on hands for approximately 30 min. Alcohol-based disinfectants seem to be very effective in killing the microorganism, while iodine-based solutions are less effective (11). During VRE outbreaks, the environment has also been shown to be highly contaminated (12). Asymptomatic stool carriage of VRE is common and contributes to the continuing propagation of the outbreak. Toilets and electronic thermometers have both been reported to be vectors for transmission (10,13).

Costly, time-consuming and cumbersome infection control techniques have been suggested to control VRE. The efficacy of glove use is well documented, but does not eliminate the need for a thorough handwashing (14). The addition of gowns is more controversial. One study (14) reported no added benefit to wearing a gown, but compliance with recommended precautions increased with gown use. Puzniak et al (15) indicated that 58 VRE cases were averted during an 18-month period when gowns were worn in addition to gloves. A mathematical model comparing different models of care showed an average of 3.81 secondary cases when no measures were in place, compared with 0.7 when standard and rigorous infection control policies were implemented. Handwashing and staff cohorting were the most important measures (16).

Implementing these measures in VRE outbreaks is cost-effective; one study demonstrated a net savings of US\$189,318 for a one-year period (17). Infection control measures have, to date, been the most effective interventions to curb VRE rates. In one institution, assigning patients to geographical cohorts, assigning nurses to patient cohorts, wearing gowns and gloves, and educating staff and patients decreased the VRE bloodstream infection rate from 2.1 patients per 1000 patient-days to 0.45 patients per 1000 patient-days ($P=0.04$). VRE colonization also decreased from 20.7 patients per 1000 patient-days to 10.3 patients per 1000 patient-days ($P<0.001$) (18).

ANTIBIOTIC USE

Several studies have explored modification of hospital formularies to decrease the prevalence of VRE (19-23). In general, the available data raise some controversy (Table 2). In an outbreak situation in a Canadian hospital, cephalosporin use was identified as the only independent risk factor for VRE (OR 13.8; 95% CI 2.5 to 76.3) (4). Quale et al (21) showed a decreased rate of VRE fecal colonization from 47% to 15% ($P<0.001$) after restricting the use of third-generation cephalosporins, clindamycin and vancomycin. A third study (20) conducted in a trauma burn unit concluded that switching from cephalosporins to piperacillin-tazobactam had a positive impact on VRE prevalence. The introduction of piperacillin-tazobactam was associated with a significant decrease of VRE in this setting (Figure 1). A very large study conducted in 126 adult ICUs in the United States from January 1996 to July 1999 indicated that higher rates of vancomycin or third-generation cephalosporin use were independently associated with VRE prevalence (22). However, other studies showed no impact on the VRE prevalence when restricting the use of third-generation cephalosporins (23). VRE

TABLE 2
Vancomycin-resistant enterococci (VRE) and antibiotics

Study	Intervention and results	Statistics
Loeb et al (4)	Case-control study of VRE colonization; cephalosporins were the only modifiable risk factor	OR 13.8 (95% CI 2.5 to 76.3)
Quale et al (21)	Restriction on vancomycin + third-generation cephalosporins; replaced third-generation cephalosporins with beta-lactamase inhibitor. VRE colonization was 47% to 15%	VRE colonization: 47% to 15% (P<0.001)
Lautenbach et al (23)	VRE prevalence increased from 17.4% to 29.6% (10 years); vancomycin and third-generation cephalosporins had little impact	P<0.001
Stiefel et al (19)	Retrospective study in four teaching hospitals; piperacillin-tazobactam was not associated with decreasing VRE rates

Figure 1) Formulary intervention: third-generation cephalosporins replaced by piperacillin-tazobactam. VRE Vancomycin-resistant enterococci. Adapted from reference 20

prevalence increased from 17.4% to 29.4% over a 10-year period in spite of a 85.8% reduction in third-generation cephalosporin use (23). The impact of antimicrobial restrictions on VRE prevalence remains unresolved. The most prudent approach is to monitor the type and the quantity of antibiotics being used, notably beta-lactams and vancomycin, on an institutional basis.

CONCLUSIONS

VRE have emerged as a major threat in many countries, but have had limited epidemiological impact in Canada. Control of this microorganism requires a multifaceted approach. Rigorous infection control measures have been proven to be efficient in controlling outbreaks. Published guidelines (3) from the Hospital Infection Control Practices Advisory Committee recommend the use of contact precautions. Some special attention has to be given to the environment in terms of cleaning. Dedicated equipment for colonized or infected patients is also recommended.

Antibiotic restriction may have a role to play but, to date, has had limited impact. The debate remains open on how to use different agents to modify VRE prevalence in institutions.

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