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Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms: A Systematic Review of the Clinical Evidence — Project Protocol

Supporting Informed Decisions

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1 CONTEXT AND POLICY ISSUES

Bacterial resistance to antibiotics is an increasing problem in Canada and the world.[1-4] Vancomycin-resistant enterococci (VRE) are strains of *Enterococcus faecium* or *Enterococcus faecalis* that contain genes resistant to vancomycin. *Escherichia coli*, *Klebsiella pneumoniae* and other gram-negative bacteria produce extended spectrum beta-lactamase (ESBL) that has the ability to inactivate beta-lactam antibiotics such as ampicillin, penicillins, and cephalosporins.

The presence and growth (colonization) of VRE and ESBL organisms in the gastrointestinal tract is a major source of infection for the carrier, and a reservoir for the transmission of VRE and ESBL to other patients.[5,6] Results from the Canadian Nosocomial Infection Surveillance Program showed that from 1999 to 2005, the rate of VRE detection and VRE infection increased from 0.37 to 1.32 cases and from 0.02 to 0.05 cases per 1,000 patients admitted to hospital respectively.[7] The Canadian Ward Surveillance Study in 2008, which examined the prevalence of anti-microbial resistant organisms in hospitals, found that ESBL-producing *Escherichia coli* were identified in all Canadian geographic regions, and that 4.9% of *Escherichia coli* isolates were ESBL producers.[8]

Prevention and control of VRE and ESBL organisms in a hospital setting include screening (a process to identify patients or health care workers at risk for being colonized with antibiotic-resistant organisms), isolation of the carriers, and decolonization (the use of topical and systemic antimicrobials to eradicate the colonization of resistant bacteria). Several hospital infection control strategies and guidelines have been developed in Canada to address prevention and control measures for antibiotic-resistant organisms.[9-13]

Practices regarding screening for VRE and ESBL organisms and isolation or decolonization of carriers vary by location, and ineffective strategies may divert resources from other areas of need. The objective of this study is to conduct a systematic review of the clinical evidence of screening, isolation, and decolonization strategies for VRE and ESBL organisms, to help standardize clinical practice. The impact of these strategies on other health services will also be examined.

2 RESEARCH QUESTIONS

1. What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients (adult and pediatric) for vancomycin-resistant enterococci (VRE) or extended spectrum beta-lactamase (ESBL) organisms?

2. What is the clinical evidence on the effectiveness of patient isolation for VRE or ESBL organisms?

3. What is the clinical evidence on the impact of isolation on the patient?

4. What is the clinical evidence for the effectiveness of decolonizing patients known to be carrying VRE or ESBL organisms?

5. What is the clinical evidence on the effectiveness of additional precautions in the operating room or post-anesthesia recovery room in patients colonized with VRE or ESBL?

6. What is the impact of screening, isolating, and decolonizing patients known to be carrying VRE or ESBL organisms on blocked beds, cancelled or limited surgeries, or the range of services a facility can provide?

3 METHODS

3.1 Literature search strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE with in-process records and daily updates through Ovid; Embase through Ovid; The Cochrane Library through Wiley; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be VRE and ESBL, and screening, isolation, and decolonization. If needed, methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval will be limited to the human population. The searches will also limited to English language documents published since January 1, 2002. Regular alerts will be established to update the search until the publication of the report. Conference abstracts will be excluded from the search results. Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). Google and other Internet search engines will be used to search for additional web-based materials.

3.2 Article selection

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen included and excluded studies. Disagreements will be resolved through discussion until consensus is reached. Duplicate publications of the same trial will be excluded unless they provide additional outcome information of interest. The study inclusion/exclusion form is provided in Appendix 1. The study selection process will be presented in a PRISMA flow chart.

Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	• Adults and pediatric patients in acute and long-term care facilities with VRE and ESBL organisms
Intervention	• Screening (targeted or universal) for VRE and ESBL organisms • Isolation for VRE and ESBL organisms • Decolonization for VRE and ESBL organisms • Contact isolation (gloves, gowns), additional cleaning, or treating colonized individuals as the last case of the day to prevent transmission to subsequent patients in the OR or PAR

Comparator	• No screening • No isolation • No decolonization • No additional precautions (contact isolation, additional cleaning, or "last case" treatment)
Outcomes	• Transmission rate, infection rate, infection rate in community versus hospital • Clinical outcomes: morbidity (including complications of VRE and ESBL organism infection), case-fatality rate, and mortality. • Adverse events: adverse effects of screening and treatment, including allergic reactions, non-allergic toxicities, medical errors, and resistance to antimicrobials. Adverse events due to isolation (such as depression). • Patient-reported outcomes: quality of care for noninfectious conditions • Health resource utilization outcomes: duration of hospitalization; blocked beds; occupied beds; cancelled or limited surgeries; ability to provide services, particularly control programs for MRSA, *Clostridium difficile*, and other antibiotic-resistant organisms.
Study design	• Randomized controlled trials (RCTs) • Non-randomized studies

ESBL = extended spectrum beta-lactamase; MRSA = methicillin-resistant *Staphylococcus aureus*; OR = operating room; PAR = post-anesthesia recovery; VRE = vancomycin-resistant enterococci.

3.3 Exclusion criteria

Articles will be excluded if they do not meet the selection criteria in Table 1, if they are published before January 2002, or if they are duplicate publications of the same study.

3.4 Data extraction and critical appraisal

A data extraction form for the clinical effectiveness review will be designed a priori to document and tabulate relevant study characteristics. Data will be extracted independently by two reviewers, and any disagreements will be resolved through discussion until consensus is reached. The validated Downs and Black checklist[14] will be used to assess the study quality of RCTs and non-randomized studies based on the quality of reporting, external validity, and risk of bias. A draft of the data extraction form for the clinical studies is provided in Appendix 2.

3.5 Data analysis methods

If trials are available, results will be pooled where applicable. If meta-analysis is deemed inappropriate due to either heterogeneity of the clinical and methodological characteristics of included studies, or absence of a comparator group, a narrative synthesis and summary of study findings will instead be conducted.

If meta-analysis is deemed appropriate, meta-analyses will be carried out using Cochrane Review Manager software[15] to derive pooled estimates of interest. If sufficient homogeneity is found across trials, all meta-analyses performed will consider a fixed effect model; if not, a random effects model will be used. Forest plots will be presented for all evidence syntheses to supplement reported estimates. Analyses of dichotomous outcomes will be summarized using relative risks (RR) and 95% confidence intervals (CI), and analyses of continuous outcomes will be summarized using mean differences and 95% CI. The chi-square test will be used to assess effect size variance, with $P < 0.10$ indicating significant heterogeneity across trials. When significant heterogeneity is identified and sufficient data are available, subgroup analyses will be

conducted to identify the primary sources of heterogeneity, such as patient characteristics and intervention procedure. Additional sensitivity analyses dealing with outlying data points, study quality, study size, and other factors will also be considered to establish the robustness of findings. If required measures of variance are found to be missing from a relevant article, the study's authors will be contacted to determine if the measure can be provided for the purposes of this investigation. If relevant data are not available, variances will be imputed where possible.

4 REFERENCES

1. Bouchillon SK, Johnson BM, Hoban DJ, Johnson JL, Dowzicky MJ, Wu DH, et al. Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant Enterococcus faecium and methicillin-resistant Staphylococcus aureus in 38 centres from 17 countries: the PEARLS study 2001-2002. Int J Antimicrob Agents. 2004 Aug;24(2):119-24.

2. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis. 2004 Sep;50(1):59-69.

3. Streit JM, Jones RN, Sader HS, Fritsche TR. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents. 2004 Aug;24(2):111-8.

4. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990-May 1999, issued June 1999. Am J Infect Control. 1999 Dec;27(6):520-32.

5. Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. Mayo Clin Proc. 2006 Apr;81(4):529-36.

6. Bush K. New beta-lactamases in gram-negative bacteria: diversity and impact on the selection of antimicrobial therapy. Clin Infect Dis. 2001 Apr 1;32(7):1085-9.

7. Ofner-Agostini M, Johnston BL, Simor AE, Embil J, Matlow A, Mulvey M, et al. Vancomycin-resistant enterococci in Canada: results from the Canadian nosocomial infection surveillance program, 1999-2005. Infect Control Hosp Epidemiol. 2008 Mar;29(3):271-4.

8. Zhanel GG, DeCorby M, Adam H, Mulvey MR, McCracken M, Lagace-Wiens P, et al. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian Ward Surveillance Study (CANWARD 2008). Antimicrob Agents Chemother [Internet]. 2010 Nov [cited 2012 Mar 7];54(11):4684-93. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976152

9. Johnston BL, Bryce E. Hospital infection control strategies for vancomycin-resistant Enterococcus, methicillin-resistant Staphylococcus aureus and Clostridium difficile. CMAJ [Internet]. 2009 Mar 17 [cited 2012 Mar 2];180(6):627-31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653571

10. Office of the Auditor General of Ontario. Prevention and control of hospital-acquired infections: special report [Internet]. Toronto: The Office; 2008 Sep. [cited 2012 Mar 2]. Available from: http://www.auditor.on.ca/en/reports_en/hai_en.pdf

11. Provincial Infectious Diseases Advisory Committee (PIDAC). Annex A – screening, testing and surveillance for antibiotic-resistant organisms (AROs). 3rd ed. Annexed to: routine practices and additional precautions in all health care settings [Internet]. Toronto: Ontario

Agency for Health Protection and Promotion; 2011 Nov. [cited 2012 Mar 2]. Available from: http://www.oahpp.ca/resources/documents/pidac/Annex%20A%20-%20CRE%20revisions%20-%20ENGLISH%20-%20FINAL%20-%202011-12-01.pdf

12. Provincial Infectious Diseases Advisory Committee (PIDAC). Best practices for infection prevention and control of resistant Staphylococcus aureus and enterococci [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2007 Mar. [cited 2012 Mar 2]. Available from: http://www.fields.utoronto.ca/programs/scientific/10-11/drugresistance/emergence/katz1.pdf

13. Provincial Infection Control Network of British Columbia (PICNet). Antibiotic resistant organisms prevention and control guidelines. [Vancouver]: PICNet; 2008 Nov.

14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2012 Mar 23];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

15. Review Manager (RevMan) [Computer program]. Version 5.1.6. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

APPENDIX A: CLINICAL STUDY INCLUSION/EXCLUSION FORM

Clinical Evidence of Screening, Isolation and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms

Title:

First author and year:
Reviewer:

INCLUSION CRITERIA:

1. **Population**: yes_____ no _____ can't tell _____
   Adults and pediatric patients in acute and long-term care facilities with VRE and ESBL organisms

2. **Intervention**: yes_____ no_____ can't tell _____
   - Screening for VRE and ESBL organisms
   - Isolation for VRE and ESBL organisms
   - Decolonization for VRE and ESBL organisms

3. **Comparator**: yes_____ no_____ can't tell _____
   - No screening
   - No isolation
   - No decolonization

4. **Outcome Measures** (any of): yes_____ no _____ can't tell _____
   - Transmission rate, infection rate, infection rate in community versus hospital
   - Health outcomes: morbidity (including complications of MRSA infection), case-fatality, mortality, quality of care for noninfectious conditions, and medical errors.
   - Adverse events: adverse effects of screening and treatment, including allergic reactions, non-allergic toxicities, medical errors, and resistance to antimicrobials. Adverse events due to isolation (depression, medical errors).
   - Length of hospital stay

5. **Study Design**: yes_____ no _____ can't tell _____
   RCTs and non-randomized studies

   - **"yes" (1-5 inclusive): include study and order full paper**_____
   - **at least one "can't tell" and others "yes" for 1-5: order full paper for further review**_____
   - **"no" (any 1-5): exclude study**

APPENDIX B: CLINICAL STUDY DATA EXTRACTION FORM

Clinical Evidence of Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms

Reviewer:

Study title:		
Author:		
ID #:	Year:	
Methods		
Study design		
Study duration		
Population: • Number of patients randomized • Number of patients completing the study		
Diagnosis		
Eligibility criteria		
Country of origin		
Industry sponsorship	☐ Yes ☐ No ☐ Unknown	
Baseline Characteristics of Study Participants		
• Age • Diagnosis • Other		
Outcomes	**Intervention**	**Comparator**
SCREENING Detection rate Colonization rate Co-colonization rate (including MRSA) Rate of VRE or ESBL organisms transmission Rate of VRE or ESBL organisms infection		

ISOLATION Rate of compliance with the use of transmission-control measures (e.g., alcohol-based sanitizing of hands, wearing gloves, cohorting) Rate of VRE or ESBL organisms transmission **DECOLONIZATION** Rate of VRE or ESBL organisms transmission: • Placebo • Drug (different dosages) Rate of VRE or ESBL organisms infection: • Placebo • Drug (different dosages) Morbidity: • Placebo • Drug (different dosages) Mortality: • Placebo • Drug (different dosages) Length of hospital stay: • Placebo • Drug (different dosages) Antimicrobial susceptibility and resistance (MIC) Drugs adverse events		
Comments		

ESBL = extended spectrum beta-lactamase; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.