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REVIEW

Controlling antibiotic resistance in intensive care units

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Abstract

Colonisation with multidrug resistant bacteria, especially resistant Gram-negatives, occurs frequently and increasingly in intensive care units (ICUs), also in the Netherlands. Infections caused by (resistant) microorganisms increase morbidity and mortality in this vulnerable patient group. This necessitates more effective control measures. Current infection control strategies include hand hygiene programs, body washing with chlorhexidine, screening plus isolation of identified carriers and selective digestive (and oral) decontamination.

Hand hygiene is generally low in ICUs. Most evidence on the effect of improved hand hygiene on infection rates stems from observational studies. However, it is likely futile to implement costly, labour-intensive interventions without optimising basic hygiene. Chlorhexidine body washing has been proven effective in reducing methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci, but not resistant Gram-negatives. Reported effects of rapid screening plus isolation are conflicting, and mostly include just MRSA. Selective digestive (and oral) decontamination reduced the 28-day mortality in Dutch ICUs in a large trial, and is considered standard of care in most ICUs in the Netherlands.

Hand hygiene, despite a lack of rigorously performed trials, should be improved in ICUs as part of normal hygienic measures. Our findings do not support the use of chlorhexidine body washing in Dutch ICUs, as MRSA prevalence is low. For patients at high risk for MRSA carriage, rapid screening can reduce unnecessary isolation days. The control of resistant Gram-negative bacteria will be a major challenge in the coming years, also in the Netherlands. We will need new methods to control the spread of these microorganisms, as current strategies have not proven effective.

Introduction

Colonisation and infection with multi-drug resistant organisms (MDRO), such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE) and highly resistant *Enterobacteriaceae* (HRE) occur with increasing frequency in hospitals worldwide, especially in intensive care units (ICUs).[1-3] In Dutch ICUs, resistance to third-generation cephalosporins has increased to 8% in E. coli and 9% in *K. pneumoniae*.[4] There is a strong increase in resistance to ciprofloxacin in P. mirabilis (7.7% in 2012) and the prevalence of highly resistant *E. coli* was 11% in 2012. Healthcare-associated infections (HCAI) caused by MDRO are associated with delayed initiation of appropriate therapy, failure of therapy, prolonged length of hospital stay, and increased morbidity and mortality.[5-8] The exact burden of HCAI is difficult to quantify because of the use of many different and partly subjective diagnostic criteria, hampering comparison of infection rates between countries and studies. In developed countries, HCAI affect up to 15% of hospitalised patients and 9 to 37% of patients in ICUs.[9-11] Consequences of HCAI for patient outcome are difficult to determine, and recent estimates suggest that the excess mortality of one of the most important HCAI, ventilator-associated pneumonia (VAP), is lower than previously assumed. Based on a meta-analysis of individual patient data from 24 randomised prevention studies, the attributable mortality of VAP was estimated to be 13%.[12] The same holds for the consequences of HCAI caused by MDRO. It is obvious that resistance has a detrimental effect on patient outcome, but recent studies reach considerably lower estimates of attributable mortality than older studies.[13] It is estimated that such infections would lead to 3.3 associated deaths per 100,000 Europeans in 2015, and that the observed increase in bacteraemia caused by HRE will become an even more pressing healthcare problem in the near future.[14-17] Hospital-acquired bacteraemia caused by MDRO

adds to the total burden of hospital-acquired bacteraemia, rather than replacing them, thus increasing to the total burden of disease.[2,18]

Bacterial colonisation is the first step in the development of HCAI.[19] Admission of colonised patients contributes to the total burden of MDRO in the ICU.[20] Acquisition of MDRO colonisation during ICU admission may occur through newly developed resistance in previously susceptible bacteria (i.e., *de novo* resistance), selection of resistant bacteria induced by antibiotic use (i.e., endogenous selection), acquisition from contaminated surfaces in the ICU, or through patient-to-patient transmission of bacteria (i.e., cross-transmission).[21] Cross-transmission mostly occurs through temporarily contaminated hands of healthcare workers.[9] Risk factors for MDRO colonisation are listed in *table 1*. The global increase in MDRO infections necessitates more effective control measures, especially in intensive care units.[5]

Table 1. Risk factors for MDRO carriage

Risk factor	MRSA	VRE	ESBL
Age	x		X
Mechanical ventilation			X
Comorbidities	x		X
Underlying immunodeficiency	x		
Severity of illness			X
Invasive devices	x		X
Previous (broad-spectrum) antibiotics	x	x	X
Previous stay in hospital, ICU or LTCF	x		X
Previous (emergency) surgery	x		X
Prolonged hospital or ICU stay		x	X
Admission for emergency abdominal surgery			X
(Surgical) wounds	x		
Haemodialysis	x		
Enteral feeding		x	
International travel			X

MDRO = multi-drug resistant organisms; MRSA = methicillin-resistant Staphylococcus aureus, VRE = vancomycin-resistant Enterococci; ESBL = extended-spectrum beta-lactamase producing Enterobacteriaceae; ICU = intensive care unit, LTCF = long-term care facilities.

Important antimicrobial resistant bacteria

Infections caused by MRSA started to increase, worldwide, in the late 1980s, and became endemic in many countries. In Dutch ICUs, MRSA infections have remained rare due to a nationwide infection control policy ('search and destroy'), which includes, amongst other things, pre-emptive isolation of patients at high risk for MRSA carriage. This program, though not based on well-designed prospective studies, has been highly successful, but the relative importance of the individual components is unknown.[22] Some European countries, such as the United Kingdom and France, have achieved impressive reductions in the incidence of HCAI caused by MRSA, but proportions of MRSA among nosocomial *S. aureus* bacteraemias remain above 25% in one-third of the countries participating in the European Antimicrobial Resistance Surveillance System (EARSS).[1]

VRE were described for the first time in Europe in 1988[23], but emerged as nosocomial pathogens in United States hospitals in the 1990s. VRE infections started to increase in European hospitals around ten years ago, and since 2011 VRE hospital outbreaks have occurred in Dutch hospitals.[24] Results from several studies suggest considerable attributable mortality of enterococcal infections, including VRE.[25]

Incidences of infections caused by resistant Gram-negative bacteria, such as extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL) have increased markedly worldwide during the past decade.[26,27] Moreover, carbapenemase-producing *Enterobacteriaceae* (CRE; notably *K. pneumoniae*) have recently emerged in different parts of the world, and represent an even bigger healthcare threat for hospitalised patients.[28-30] All *Enterobacteriaceae* resistant to at least third-generation cephalosporins, including ESBL and CRE, are considered highly resistant *Enterobacteriaceae* (HRE).

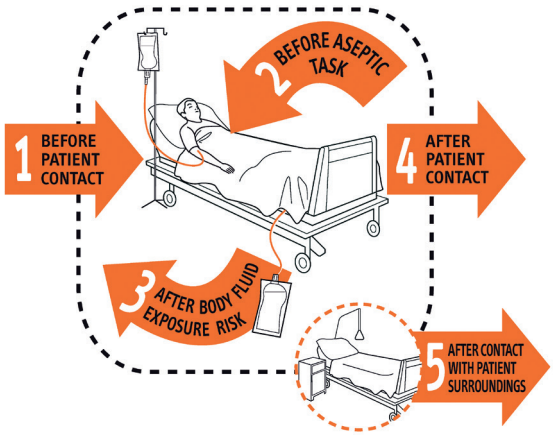
ESBLs and most genes conferring carbapenemase production are plasmid-mediated, which allows efficient transfer of resistance to other bacteria.[26] Furthermore, the different genes can be associated with different resistance phenotypes, hampering rapid detection in laboratories. These aspects complicate infection control strategies, especially in healthcare facilities. In the Netherlands, 5 to 10% of all Enterobacteriaceae causing bacteraemia harbour ESBL genes. Many of these isolates are also resistant to ciprofloxacin and aminoglycosides, and these figures are expected to increase in the coming years. The increased occurrence of infections caused by ESBL-producing bacteria coincides with an increased use of carbapenems.[4]

Current strategies to combat antibiotic resistance in the ICU

Current strategies to control the spread of antibiotic resistance include hand hygiene programs, the use of chlorhexidine body washing, nasal decontamination with mupirocin (for MRSA only) and screening of patients on admission with contact precautions of identified carriers. All these interventions aim to interrupt cross-transmission of bacteria. Often, these interventions are combined in a variety of 'infection control bundles'.

Improving hand hygiene is considered a cornerstone of infection prevention. There is a firm body of evidence that low hand hygiene compliance is associated with higher bacterial transmission rates as well as increased incidence of HCAI.[9] However, this evidence mainly stems from observational studies. Multiple studies have reported low compliance levels for hand hygiene, especially in ICUs.[31]

Figure 1. WHO 'My 5 Moments for Hand Hygiene'



In 2009, the World Health Organisation (WHO) presented its *Guidelines on Hand Hygiene in Healthcare*, which included a multimodal hand hygiene improvement strategy ('My 5 Moments for Hand Hygiene', *figure 1*), with guidance for training, observation, and performance reporting across different healthcare settings. This method, combined with a feedback intervention using behavioural theory, improved hand hygiene adherence by 7-9%; and audit and feedback were considered essential for its success.[32] It is questionable whether hand hygiene as a single control measure will be sufficient to control transmission of MDRO[33], yet implementing other more costly and labour-intensive interventions without optimising hygiene is likely futile.

Chlorhexidine body washing has been associated with lower infection rates, especially in ICUs.[34-41] However, the evidence coming from studies published before 2013 was weakened by inter-study differences in chlorhexidine use, co-interventions, and patient case-mix. Based on a systematic review, it was concluded that there was evidence that chlorhexidine body washing reduced carriage and possibly bloodstream infections with MRSA and VRE in ICU patients, but there was no evidence for an effect on carriage or infections with HRE.[42]

A third strategy is to treat MDRO carriers with contact precautions or in single-patient rooms.[43-44] This reduces the likelihood of cross-transmission and its effectiveness could be improved with faster detection of carriage.[45-48] However, reported effects of rapid screening for MDRO carriage (mostly MRSA) followed by contact precautions are conflicting, and preclude evidence-based recommendations.[49]

Two previous studies failed to demonstrate beneficial incremental effects of screening on ICU admission and contact precautions for identified carriers of MDRO.[50,51] However, these studies addressed Gram-positive bacteria only, and were criticised for not evaluating interventions based on rapid screening, as average turn-around times of cultures were 3 days[50] and 5.2 days[51], respectively, implying that many screening results were not available before patient discharge. Furthermore, failure of isolation was accredited to a low 21% hand hygiene compliance in one study.[50] In the Netherlands, pre-emptive isolation of high-risk patients (e.g. patients transferred from a foreign hospital) is used as part of the 'search and destroy' strategy. In a Dutch study, rapid testing of such patients by either PCR or chromogenic screening reduced the number of unnecessary isolation days by 60% and 47%, respectively.[52]

Three recent cluster randomised studies have evaluated similar interventions. Climo et al. compared daily bathing with chlorhexidine-impregnated washcloths to non-antimicrobial washcloths in a cluster-randomised crossover design in nine ICUs.[53] The intervention was aimed at Gram-positive MDRO only, and reduced acquisition of VRE, but not MRSA. A reduction in primary bloodstream infection, mainly coagulase-negative staphylococci bacteraemia, was demonstrated. However, the analysis did not account for clustering effects and may therefore have overestimated the statistical significance of the findings.

In a second study, 74 ICUs were cluster-randomised to either MRSA screening and isolation, targeted decolonisation, or universal decolonisation with chlorhexidine body washing combined with mupirocin nasal ointment. Universal decolonisation was associated with significant reductions in clinical cultures yielding MRSA, and in all-cause, but not MRSA, bacteraemia.[54]

A third study investigated the effect of improved hand hygiene combined with chlorhexidine body washing ('optimal hygiene') in an interrupted time-series design. After this intervention, the incremental effect of screening and isolation of identified carriers by either chromogenic agar or molecular methods was investigated in a cluster-randomised design.[55] In this trial in 13 European ICUs, optimal hygiene was associated with a 3.6% weekly reduction of MRSA acquisition. There was a trend towards a similar effect on VRE acquisition, but no such trend was observed for HRE acquisition. These findings suggest that patient-to-patient transmission may not be the dominant acquisition route for HRE in ICU patients, and other prevention methods will be needed, such as antibiotic stewardship programs or intestinal decolonisation with non-absorbable antibiotics.[49,56-59] Adding screening and isolation of carriers, by either chromogenic agar or molecular methods, failed to further reduce acquisition rates. In the largest study to date, intestinal decolonisation with non-absorbable antibiotics reduced 28-day mortality by 13% (selective digestive decontamination) and 11% (selective oral decontamination) respectively, in Dutch ICUs.[57] This strategy is now considered standard care in most Dutch ICUs.

Conclusions

Controlling resistance in the ICU remains challenging. We recommend using the WHO '5 moments' program in all Dutch ICUs.[9] Our findings do not support the use of chlorhexidine body washing in Dutch ICUs, as MRSA prevalence is low. For patients at high risk of MRSA carriage, rapid screening by either PCR or chromogenic methods can be used to reduce unnecessary isolation days.[52] The control of HRE, and especially carbapenemase-producing strains that are increasingly causing infections worldwide[27-30], will be a major challenge in the coming years, also in the Netherlands.4 Patient-to-patient transmission may not be the most important route of acquisition, and preliminary investigations suggest different transmissibility for different species.[60-61] If further analyses confirm these differences, this might justify a pathogen-specific infection control approach for HRE. Screening and isolation of HRE carriers, though widely used, has not been proven to be effective.[55] These findings suggest that new methods to control HRE – e.g. selective digestive decontamination – should be investigated even in settings with endemic resistance. In Dutch ICUs, this is already considered standard of care.

References

1. ECDC. Annual epidemiological report on communicable diseases in Europe 2010. Stockholm: European Centre for Disease Prevention and Control, 2010. Available from: http://www.ecdc.europa.eu/en/publications/publications/1011_sur_annual_epidemiological_report_on_communicable_diseases_in_europe.pdf.
2. de Kraker MEA, Jarlier V, Monen JCM, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. Clin Microbiol Infect. 2013;19:860-8..
3. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Ann Int Care Med. 2011;1:1-7.
4. RIVM. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. 2013 [cited 2014 July 7]. Available from: http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2013/Antibioticaresistentie_in_Nederland_neemt_toe.
5. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, et al. Strategies to Prevent and Control the Emergence and Spread of Antimicrobial-Resistant Microorganisms in Hospitals. A challenge to hospital leadership. JAMA. 1996;275:234-40.
6. Kollef MH. Inadequate Antimicrobial Treatment: An Important Determinant of Outcome for Hospitalized Patients. Clin Infect Dis. 2000;31 Suppl 4:S131-8.
7. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and healthcare costs. Clin Infect Dis. 2006;42 Suppl 2:S82-9.
8. Jones RN. Global epidemiology of antimicrobial resistance among community-acquired and nosocomial pathogens: a five-year summary from the SENTRY Antimicrobial Surveillance Program (1997-2001). Semin Respir Crit Care Med. 2003;24:121-34.
9. World Health Organization. WHO Guidelines on Hand Hygiene in Healthcare. 2009. Available from: http://whqlibdoc.who.int/publications/2009/9789241597906_eng.pdf.
10. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA. 1995;274:639-44.
11. Vincent J. Nosocomial infections in adult intensive-care units. Lancet. 2003;361:2068-77.
12. Melsen WG, Rovers MM, Groenwold RHH, Bergmans DCJJ, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis. 2013;13:665-71.
13. Lambert M-L, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, et al. Clinical outcomes of healthcare-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis. 2011;11:30-8.
14. de Kraker MEA, Davey PG, Grundmann H, BURDEN study group. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med. 2011;8:e1001104.
15. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrob Agents Ch. 2011;55:1598-605.
16. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 2011;66:398-407.
17. Gagliotti C, Balode A, Baquero F, Degener J, Grundmann H, Gür D, et al. Escherichia coli and Staphylococcus aureus: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. European Centre for Disease Prevention and Control, 2011.
18. Ammerlaan HSM, Herwaldt L. Trends in nosocomial MRSA bacteraemias: addition or replacement? PhD thesis: The clinical impact of methicillin-resistant Staphylococcus aureus on morbidity, mortality, and burden of disease. 2010.
19. Bonten MJM, Weinstein RA. The role of colonization in the pathogenesis of nosocomial infections. Infect Control Hosp Epidemiol. Infect Control Hosp Edidemiol. 1996;17:193-200.
20. Bonten MJM, Mascini EM. The hidden faces of the epidemiology of antibiotic resistance. Intensive Care Med. 2003;29:1-2.
21. Nijssen S, Fluit A, Vijver D, Top J, Willems R, Bonten MJM. Effects of reducing beta-lactam antibiotic pressure on intestinal colonization of antibiotic-resistant gram-negative bacteria. Intensive Care Med. 2009;36:512-9.
22. Bootsma MCJ, Diekmann O, Bonten MJM. Controlling methicillin-resistant Staphylococcus aureus: quantifying the effects of interventions and rapid diagnostic testing. Proceedings of the National Academy of Sciences. National Acad Sciences. 2006;103:5620-5.

23. Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-Mediated Resistance to Vancomycin and Teicoplanin in Enterococcus Faecium. N Engl J Med. 198821;319:157-61.
24. Bonten MJM, Willems RJ. Vancomycin-resistant enterococcus--chronicle of a foretold problem. Ned Tijdschr Geneeskd. 2012;156:A5233.
25. Bearman GM, Wenzel RP. Bacteremias: A Leading Cause of Death. Arch Med Res. 2005;36:646-59.
26. Goossens H, Grabein B. Prevalence and antimicrobial susceptibility data for extended-spectrum β-lactamase- and AmpC-producing Enterobacteriaceae from the MYSTIC Program in Europe and the United States (1997-2004). Diagn Micr Infec Dis. 2005;53:257-64.
27. Razazi K, Derde LPG, Verachten M, Legrand P, Lesprit P, Brun-Buisson C. Clinical impact and risk factors for colonization with extended-spectrum β-lactamase-producing bacteria in the intensive care unit. Intensive Care Med. 2012;38:1769-78.
28. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-beta-lactamases: the quiet before the storm? Clin Microbiol Rev. 2005;18:306-25.
29. Walsh TR. Emerging carbapenemases: a global perspective. Int J Antimicrob Ag. 2010;36:S8-14.
30. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect. 2012;18:413-31.
31. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Infection Control Program. Ann Int Med. 1999;130:126-30.
32. Fuller C, Michie S, Savage J, McAteer J, Besser S, Charlett A, et al. The Feedback Intervention Trial (FIT) — Improving Hand-Hygiene Compliance in UK Healthcare Workers: A Stepped Wedge Cluster Randomised Controlled Trial. Cowling BJ, editor. PLoS ONE. 2012;7:e41617.
33. Sepkowitz KA. Why doesn't hand hygiene work better? Lancet Infect Dis. 2012;12:96-7.
34. Batra R, Cooper BS, Whiteley C, Patel AK, Wyncoll D, Edgeworth JD. Efficacy and Limitation of a Chlorhexidine-Based Decolonization Strategy in Preventing Transmission of Methicillin-Resistant Staphylococcus aureus in an Intensive Care Unit. Clin Infect Dis. 2010;50:210-7.
35. Bleasdale SC, Trick WE, Gonzalez IM, Lyles RD, Hayden MK, Weinstein RA. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. Arch Intern Med. Am Med Assoc; 2007;167:2073.
36. Camus C, Bellissant E, Sebille V, Perrotin D, Garo B, Legras A, et al. Prevention of acquired infections in intubated patients with the combination of two decontamination regimens. Crit Care Med. 2005;33:307-14.
37. Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK, Perl TM, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and healthcare-associated bloodstream infections: Results of a quasi-experimental multicenter trial. Crit Care Med. 2009;37:1858-65.
38. Gould IM, MacKenzie FM, MacLennan G, Pacitti D, Watson EJ, Noble DW. Topical antimicrobials in combination with admission screening and barrier precautions to control endemic methicillin-resistant Staphylococcus aureus in an Intensive Care Unit. Int J Antimicrob Ag. 2007;29:536-43.
39. Popovich KJ, Hota B, Hayes R, Weinstein RA, Hayden MK. Daily skin cleansing with chlorhexidine did not reduce the rate of central-line associated bloodstream infection in a surgical intensive care unit. Intensive Care Med. 2010;36:854-8.
40. Raineri E, Crema L, De Silvestri A, Acquarolo A, Albertario F, Carnevale G, et al. Meticillin-resistant Staphylococcus aureus control in an intensive care unit: a 10 year analysis. J Hosp Infect. 2007;67:308-15.
41. O'Horo JC, Silva GLM, Munoz-Price LS, Safdar N. The efficacy of daily bathing with chlorhexidine for reducing healthcare-associated bloodstream infections: a meta-analysis. Infect Control Hosp Epidemiol. 2012;33:257-67.
42. Derde LPG, Dautzenberg MJD, Bonten MJM. Chlorhexidine body washing to control antimicrobial-resistant bacteria in intensive care units: a systematic review. Intensive Care Med. 2012;38:931-9.
43. Montecalvo MA, Jarvis WR, Uman J, Shay DK, Petrullo C, Rodney K, et al. Infection-Control Measures Reduce Transmission of Vancomycin-Resistant Enterococci in an Endemic Setting. Ann Int Med. American College of Physicians; 1999;131:269-72.
44. Huang SS, Yokoe DS, Hinrichsen VL, Spurchise LS, Datta R, Irina Miroshnik ARP. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis. 2006;43:971-8.
45. Malhotra-Kumar S, Haccuria K, Michiels M, Ieven M, Poyart C, Hryniewicz W, et al. Current trends in rapid diagnostics for methicillin-resistant Staphylococcus aureus and glycopeptide-resistant enterococcus species. J Clin Microbiol. 2008;46:1577-87.
46. Malhotra-Kumar S, Van Heirstraeten L, Lee A, Abrahantes JC, Lammens C, Vanhommerig E, et al. Evaluation of molecular assays for rapid detection of methicillin-resistant Staphylococcus aureus. J Clin Microbiol. 2010;48:4598-601.
47. Gazin M, Paasch F, Goossens H, Malhotra-Kumar S, on behalf of the MOSAR WP2 and SATURN WP1 Study Teams. Current Trends in Culture-Based and Molecular Detection of Extended-Spectrum- -Lactamase-Harboring and Carbapenem-Resistant Enterobacteriaceae. J Clin Microbiol. 2012;50:1140-6.
48. Gazin M, Lammens C, Goossens H, Malhotra-Kumar S, on behalf of the MOSAR WP2 Study Team. Evaluation of GeneOhm VanR and Xpert vanA/vanB molecular assays for the rapid detection of vancomycin-resistant enterococci. Eur J Clin Microbiol Infect Dis. 201112;31:273-6.
49. Cooper BS. Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. BMJ. 2004;329:533-40.
50. Cepeda JA, Whitehouse T, Cooper BS, Hails J, Jones K, Kwaku F, et al. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. Lancet. 2005;365:295-304.
51. Huskins WC, Huckabee CM, O'Grady NP, Murray P, Kopetskie H, Zimmer L, et al. Intervention to reduce transmission of resistant bacteria in intensive care. N Engl J Med. 2011;364:1407-18.
52. Wassenberg MWM, Kluytmans JAJW, Box ATA, Bosboom RW, Buiting AGM, Van Elzakker EPM, et al. Rapid screening of methicillin-resistant Staphylococcus aureus using PCR and chromogenic agar: a prospective study to evaluate costs and effects. Clin Microbiol Infect. 2010;16:1754-61.
53. Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, et al. Effect of Daily Chlorhexidine Bathing on Hospital-Acquired Infection. N Engl J Med 20137;368:533-42.
54. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus Universal Decolonization to Prevent ICU Infection. N Engl J Med. 2013;368:2255-65.
55. Derde LPG, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJL, Gniadkowski M, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis. 2014;14:31-9.
56. Eliopoulos GM, Shardell M, Harris AD, El-Kamary SS, Furuno JP, Miller RR, et al. Statistical Analysis and Application of Quasi Experiments to Antimicrobial Resistance Intervention Studies. Clin Infect Dis. 2007;45:901-7.
57. de Smet AMGA, Kluytmans JAJW, Cooper BS, Mascini EM, Benus RFJ, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med. 2009;360:20-31.
58. Oostdijk EAN, de Smet AMGA, Blok HEM, Thieme Groen ES, van Asselt GJ, Benus RFJ, et al. Ecological Effects of Selective Decontamination on Resistant Gram-negative Bacterial Colonization. Am J Respir Crit Care Med. 2010;181:452-7.
59. Oostdijk EAN, de Smet AMGA, Kesecioglu J, Bonten MJM, Dutch SOD-SDD Trialists Group. Decontamination of cephalosporin-resistant Enterobacteriaceae during selective digestive tract decontamination in intensive care units. J Antimicrob Chemother. 2012;67:2250-3.
60. Harris AD, Perencevich EN, Johnson JK, Paterson DL, Morris JG, Strauss SM, et al. Patient-to-patient transmission is important in extended-spectrum beta-lactamase-producing Klebsiella pneumoniae acquisition. Clin Infect Dis. 2007;45:1347-50.
61. Guet-Revillet H, Le Monnier A, Breton N, Descamps P, Lecuyer H, Alaabouche I, et al. Environmental contamination with extended-spectrum β-lactamases: Is there any difference between Escherichia coli and Klebsiella spp? AmJ Infect Control. 2012;40:845-8.